VOL. 33 DECEMBER 1957 NO. 12

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

PAUL DUDLEY WHITE

JOSEPH C. HINSEY

PERRIN H. LONG

THERAPY OF DISEASES OF THE GALLBLADDER AND BILE DUCTS

Transcription of a Panel Meeting on Therapeutics

J. RUSSELL TWISS ALBERT F. R. ANDRESEN

FRANKLIN M. HANGER HOWARD A. PATTERSON

WILLIAM H. SHEHADI

NEW YORK PATHOLOGICAL SOCIETY

just two tablets
at bedtime

for gratifying
rauwolfia response
virtually free from side actions

Rauwiloid®

Riker
LOS ANGELES

increased strides

in rheumatoid arthritis

on only 12 mg. daily average maintenance dosage†

METICORTELONE®

prednisolone

..rapidly reduces swelling, tenderness and pain on motion

..overcomes disabling muscle spasm

..maintains therapeutic benefits by minimizing sodium retention, edema and hypokalemia associated with older corticosteroids

†in rheumatoid arthritis—daily maintenance dosage averages only 12 mg. (may be as low as 5 mg.) after initial suppression of symptoms

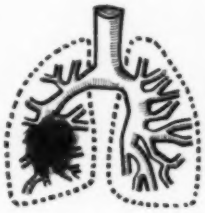
*"Meti"*steroids mean minimal maintenance dosage*

dosage: In rheumatoid arthritis—initially 20 to 30 mg. a day until favorable response is obtained. Dosage is gradually reduced by 2.5 to 5 mg. daily until maintenance levels between 5 and 20 mg. are reached. Buff-colored tablets of 1, 2.5 and 5 mg.

*T.M. SL-F-10107

Schering

For the complications of Asian flu



GANTRICILLIN

provides Gantrisin plus penicillin in a single tablet....

for control of both gram-positive and gram-negative secondary invaders.

Gantricillin 300 for potent therapy

Gantricillin Acetyl 200 suspension for pediatric use

Gantricillin 100 for mild infections

Gantricillin®; Gantrisin®-brand of sulfisoxazole

ROCHE LABORATORIES
DIVISION OF HOFFMANN-LA ROCHE INC
Nutley 10 · New Jersey

The Bulletin of The New York Academy of Medicine, Vol. 33, No. 12, December, 1957. Published Monthly by The New York Academy of Medicine, 2 East 103 Street, New York 29, N. Y. Entered as second-class matter February 3, 1928, at the Post Office at New York, N. Y., under the Act of August 24, 1912. Annual subscription United States and Canada $8.00. All other countries $9.00. Single copies 90c.

PICK THE PIPERIDOL
BEST FOR YOUR PATIENT

for pain⇄spasm of the upper G.I. tract

capsule
DACTIL®
Brand of Piperidolate HCl

visceral eutonic
relieves gastroduodenal and biliary pain⇄spasm —usually in 10 minutes

for peptic ulcer

tablet
PIPTAL®
Brand of Pipenzolate Methylbromide

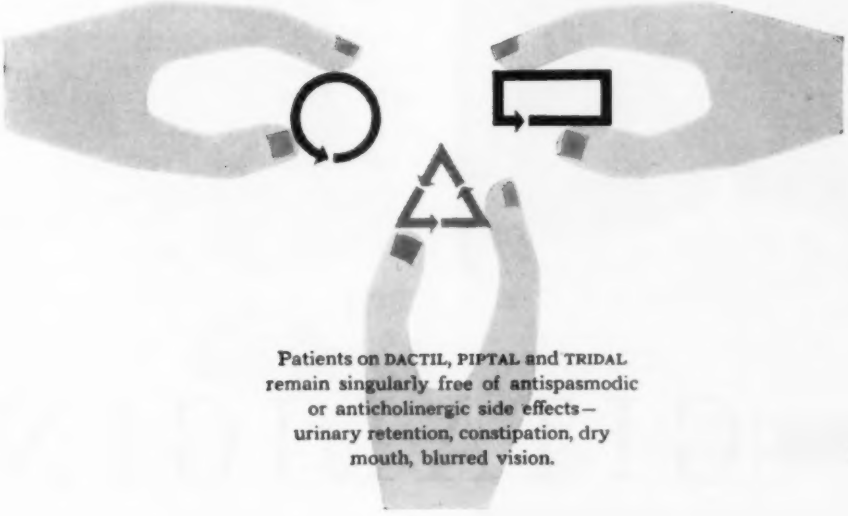
cholinolytic
normalizes motility *and* secretion; prolongs remissions, curbs recurrences

for generalized G.I. disorders

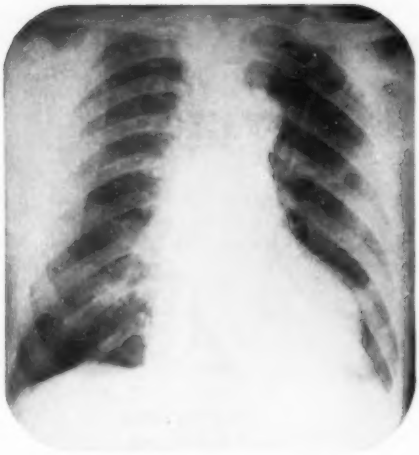
tablet
TRIDAL®
(DACTIL + PIPTAL—in one tablet)

rapid, prolonged relief *throughout the G.I. tract*

LAKESIDE



Patients on DACTIL, PIPTAL and TRIDAL remain singularly free of antispasmodic or anticholinergic side effects—urinary retention, constipation, dry mouth, blurred vision.



VISUAL HEART CLINIC — ONE OF A SERIES ARTERIOSCLEROTIC HEART DISEASE

ROENTGEN CONFIGURATION

Postero-anterior position

Moderate left ventricular enlargement with prominence and calcification of aortic knob.

Taken from White Laboratories' Technical Exhibit, American Medical Association, 105th Annual Meeting, Chicago, June 11-15, 1956.

"Safe and effective maintenance therapy with digitalis glycosides had been a problem at our institution until we used gitalin [GITALIGIN]..."*

- *Safest—the only cardioactive glycoside whose therapeutic dose is ⅓ its toxic dose.*
- *Moderate rate of elimination.*
- *Short latent period.*
- *Uniform clinical potency.*

Patients now on other cardiotonics may be easily maintained on Gitaligin: 0.5 mg. of Gitaligin is approximately equivalent to 0.1 Gm. digitalis leaf, 0.1 mg. digitoxin, 0.5 mg. digoxin.

GITALIGIN TABLETS — Bottles of 30, 100 and 1000.

GITALIGIN DROPS — 30 cc. bottles with dropper calibrated for 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5 mg.

now available

GITALIGIN INJECTION — 5 cc. ampuls containing 2.5 mg. (0.5 mg. per cc.) of Gitaligin. Packages of 3 and 12 ampuls.

*HARRIS, R., AND DEL GIACCO R. R.: AM HEART J. (AUG.) 1956. BIBLIOGRAPHY ON REQUEST

White's

GITALIGIN®

(WHITE'S BRAND OF AMORPHOUS GITALIN)

White Laboratories, Inc. • Kenilworth, New Jersey

SANBORN MODEL 300 VISETTE

ELECTROCARDIOGRAPH

modern components, construction give greater durability

The transistors, printed wiring panels and smaller galvanometer that help make the new 18 pound VISETTE ecg the size of a brief case also make possible another — and equally important — advantage: *ruggedness*. Metal-encased transistors, most of them smaller than a pencil eraser, are used in place of many vacuum tubes in the Visette circuit; they can withstand extreme jolts, jars and vibration without damage. And instead of dozens of connections which would ordinarily be made with wire, conductive paths are *printed* on small, rigid phenolic panels. The Visette's direct-writing galvanometer, too, is designed for increased resistance to both physical and electrical hazards. The rigid metal frame and chassis, to which all units are anchored, is then housed in an outer case of high impact Royalite, reinforced with metal strips at points of greatest strain.

Here is *true* portability — a carefully designed combination of *light weight* (that every nurse and technician will appreciate); *small size* (that requires the same space on your desk as a letterhead); and *ruggedness*, that assures continued accuracy of operation after countless trips in your car, on hospital and house calls, wherever your Visette is required. Handy "companions" for the Visette include a protective vinyl Weather Cover, and a compact, attractive table for office use of the Visette.

You *can* take it with you — *with confidence.*

18 lbs.
TRANSISTORIZED
$625 del.

An informative four-page folder describes and pictures all major characteristics of the new Model 300 Visette electrocardiograph. Copies available on request.

40th ANNIVERSARY 1917-1957

SANBORN COMPANY
MEDICAL DIVISION

175 Wyman St., Waltham 54, Mass.

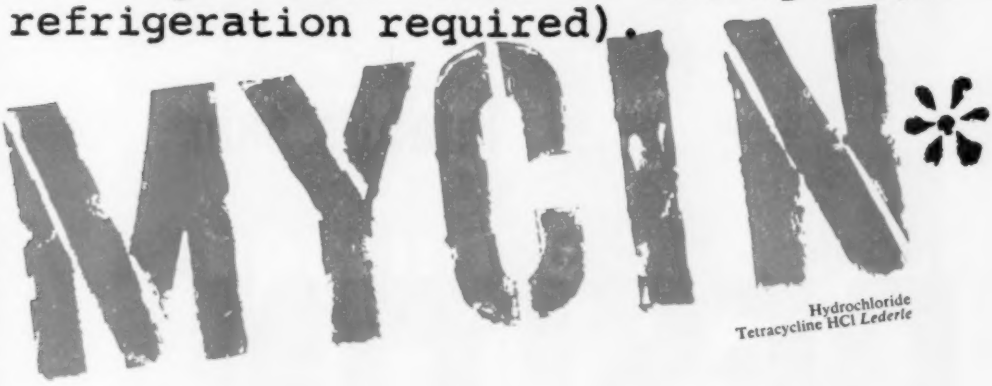
INTRAVENOUS Compatible with common IV fluids. Stable for 24 hours in solution at room temperature. Average IV dose is 500 mg. given at 12 hour intervals. Vials of 100 mg., 250 mg., 500 mg.

ACHRO

THERAPEUTIC BLOOD LEVELS ACHIEVED

Many physicians advantageously use the parenteral forms of ACHROMYCIN in establishing immediate, effective antibiotic concentrations. With ACHROMYCIN you can expect prompt

INTRAMUSCULAR Used to start a patient on his regimen immediately, or for patients unable to take oral medication. Convenient, easy-to-use, ideally suited for administration in office or patient's home. Supplied in single dose vials of 100 mg., (no refrigeration required).



IN MINUTES -- SUSTAINED FOR HOURS

control, with minimal side effects, over a wide variety of infections - reasons why ACHROMYCIN is one of today's foremost antibiotics.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK

*REG. U. S. PAT. OFF.

an important
first step
in the care
of the
infant's skin

DESITIN®
OINTMENT

No other product is more effective in healing the baby's skin and keeping it clear, smooth, supple, and free from

diaper rash • dermatitis • intertrigo
heat rash • chafing • irritation • excoriation

Soothing, protective, healing[1-5] Desitin Ointment — ***rich in cod liver oil*** — is the most widely used ethical specialty for the over-all care of the infant's skin.

May we send ***samples*** and literature?

DESITIN CHEMICAL COMPANY, Providence, R. I.

1. Grayzel, H. G., Heimer, C. B., and Grayzel, R. W.: New York St. J. Med. 53:2233, 1953. 2. Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951. 3. Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Ind. Med. & Surgery 18:512, 1949. 4. Sobel, A. E.: Scientific Exhibit, A.M.A. Meet. 1955. 5. Marks, M. M.: Missouri Med. 52:187, 1955.

Tubes of 1 oz., 2 oz., 4 oz., and 1 lb. jars.

an oxazine . . . not an amphetamine
appetite curbed . . .
sleep undisturbed
PRELUDIN
developed specifically
for appetite suppression
Chemically different from the amphetamines, PRELUDIN provides potent appetite suppression with little or no central stimulation.
• rarely causes loss of sleep[1] — may be given late enough in the day to curtail after-dinner "nibbling," yet not hinder sleep.
• avoids nervous tension and "jitters"[2] — simultaneous sedation is not required.[3]
". . . in clinical use the side-effects of nervousness, hyperexcitability, euphoria, and insomnia are much less than with the amphetamine compounds and rarely cause difficulty."[4]
References: (1) Gelvin, E. P., McGavack, T. H., and Kenigsberg, S.: Am. J. Digest. Dis. 1:155, 1956. (2) Holt, J. O. S., Jr.: Dallas M. J. 42:497, 1956. (3) Notenshon, A. L.: Am. Pract. & Digest Treat. 7:1456, 1956. (4) Council on Pharmacy and Chemistry, New and Nonofficial Remedies: J.A.M.A. 163:356 (Feb. 2) 1957.
PRELUDIN® (brand of phenmetrazine hydrochloride). Scored, square, pink tablets of 25 mg. Under license from C. H. Boehringer Sohn, Ingelheim.
GEIGY Ardsley, New York

"Milpath" two-level control of gastrointestinal dysfunction

Miltown® + *anticholinergic*

at the central level The tranquilizer Miltown® reduces anxiety and tension.[1, 3, 6, 7] Unlike the barbiturates, it does not impair mental or physical efficiency.[5, 7]

at the peripheral level The anticholinergic tridihexethyl iodide reduces hypermotility and hypersecretion.

Unlike the belladonna alkaloids, it rarely produces dry mouth or blurred vision.[2, 4]

indications: peptic ulcer, spastic and irritable colon, esophageal spasm, G. I. symptoms of anxiety states.

each "Milpath" tablet contains:

Miltown® (meprobamate WALLACE) ..... 400 mg.
(2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate)

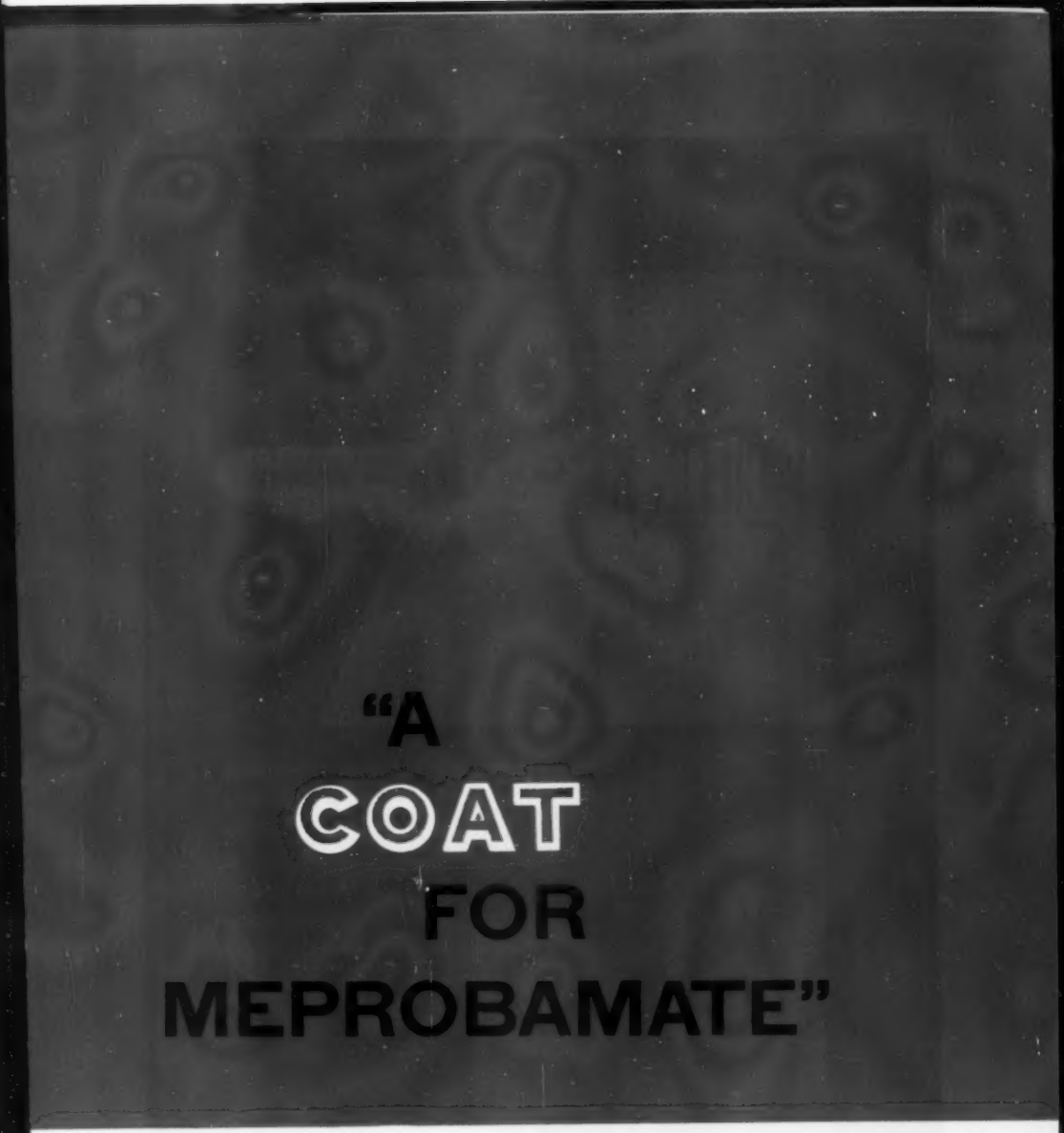
Tridihexethyl iodide ..... 25 mg.
(3-diethylamino-1-cyclohexyl-1-phenyl-1-propanol-ethiodide)

dosage: 1 tablet t.i.d. at mealtime and 2 tablets at bedtime.

available: bottles of 50 scored tablets.

references: 1. Altschul, A. and Billow, B.: The clinical use of meprobamate, (Miltown®), New York J. Med. *57*: 2361, July 15, 1957. 2. Atwater, J. S.: The use of anticholinergic agents in peptic ulcer therapy. J. M. A. Georgia *45*:421, Oct. 1956. 3. Borrus, J. C.: Study of effect of Miltown (2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate) on psychiatric states. J. A. M. A. *157*:1596, April 30, 1955. 4. Cayer, D.: Prolonged anticholinergic therapy of duodenal ulcer. Am. J. Digest. Dis. *1*:301, July 1956. 5. Marquis, D. G., Kelly, E. L., Miller, J. G., Gerard, R. W. and Rapoport, A.: Experimental studies of behavioral effects of meprobamate on normal subjects. Ann. New York Acad. Sc. *67*:701, May 9, 1957. 6. Phillips, R. E.: Use of meprobamate (Miltown®) for the treatment of emotional disorders. Am. Pract. & Digest Treat. *7*:1573, Oct. 1956. 7. Selling, L. S.: A clinical study of Miltown®, a new tranquilizing agent. J. Clin. & Exper. Psychopath. *17*:7, March 1956. 8. Wolf, S. and Wolff, H. G.: Human Gastric Function, Oxford University Press, New York, 1947

WALLACE LABORATORIES, New Brunswick, N. J.



"Meprotabs" are new, *coated*, white, unmarked 400 mg. tablets of meprobamate. ■ "Meprotabs" are pleasant tasting, and easy to swallow. ■ In this new form, the nature of medication is not identifiable by the patient. ■ "Meprotabs" are indicated for the relief of anxiety, tension and muscle spasm in everyday practice. ■ *Usual dosage:* One or two tablets t.i.d.

"Meprotabs"

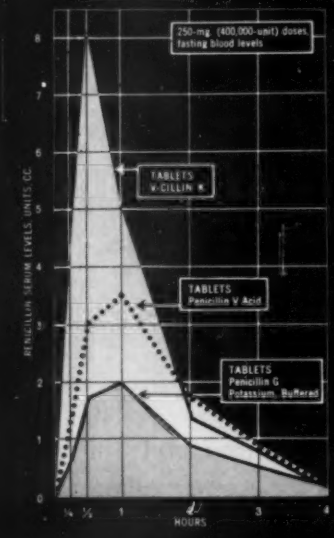
(2-methyl-2-n-propyl-1,3-propanediol dicarbamate)

WALLACE LABORATORIES, *New Brunswick, N. J.*

V-CILLIN K

(Penicillin V Potassium, Lilly)

New key to oral penicillin effectiveness



Within 15 to 30 minutes, high blood levels are produced by 'V-Cillin K,' a new, readily soluble form of clinically proved 'V-Cillin' (Penicillin V, Lilly). It combines the virtue of acid stability with greater solubility. Because it is more soluble, 'V-Cillin K' is easily and quickly absorbed. At pharmacies everywhere.

Available in tablets of 125 and 250 mg.

Lilly

QUALITY / RESEARCH / INTEGRITY

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U. S. A.

733154

SECOND SERIES DECEMBER 1957 VOL. 33, NO. 12

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

CONTENTS

The Epidemiology of Heart Disease 819
Paul Dudley White

Present Status of the Full-Time System 838
Joseph C. Hinsey, Ph.D.

Problems in Medical Education 849
Perrin H. Long

Therapy of Diseases of the Gallbladder and Bile Ducts 859
Transcription of a Panel Meeting on Therapeutics
J. Russell Twiss, Albert F. R. Andresen, Franklin M. Hanger, Howard A. Patterson and William H. Shehadi

A Communication to the Fellows of The New York Academy of Medicine 883

New York Pathological Society: Abstracts 885

Index, Volume 33, 1957 897

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

Annual subscription United States and Canada $8.00. All other countries $9.00. Single copies 90c.
ADVERTISING OFFICE • 30 ROCKEFELLER PLAZA, N. Y. C. 20 • CIrcle 7-7706
Copyright, 1957 by The New York Academy of Medicine

OFFICERS AND STAFF OF THE ACADEMY

1957

President

ROBERT L. LEVY

Vice-Presidents

ALBERT H. ALDRIDGE — HAROLD BROWN KEYES — DAVID P. BARR

Treasurer

SHEPARD KRECH

Recording Secretary

FREDERICK H. WILKE

Trustees

GEORGE BAEHR
STUART L. CRAIG
CONDICT W. CUTLER, JR.
*SHEPARD KRECH
*ROBERT L. LEVY
WILLIAM F. MACFEE
HAROLD R. MIXSELL
WILLIAM BARCLAY PARSONS
HENRY ALSOP RILEY
BENJAMIN P. WATSON
JEROME P. WEBSTER
ORRIN S. WIGHTMAN
*FREDERICK H. WILKE

Council

The President — The Vice-Presidents — The Trustees
The Treasurer — The Recording Secretary
The Chairmen of Standing Committees

Director

HOWARD REID CRAIG

Librarian

GERTRUDE L. ANNAN

Executive Secretary
Committee on Public Health

HARRY D. KRUSE

Executive Secretary
Committee on Medical Education

ROBERT L. CRAIG

Executive Secretary
Committee on Medical Information

IAGO GALDSTON

Comptroller

ARTHUR A. EBERLE

Legal Counsel

DAVIS POLK WARDWELL SUNDERLAND & KIENDL

Library Consultants

JANET DOE, B. W. WEINBERGER, CURT PROSKAUER

EDITORIAL BOARD

JEROME P. WEBSTER, *Chairman*
GERTRUDE L. ANNAN
DAVID P. BARR
MARGARET BEVANS
JOHN G. KIDD
ROBERT F. LOEB
LOUIS M. ROUSSELOT
KARL VOGEL

ROBERT L. CRAIG, *Secretary and Editor*

* Ex-Officio

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 33, NO. 12 DECEMBER 1957

THE EPIDEMIOLOGY OF HEART DISEASE*

HOW CAN WE PROTECT OUR YOUTH OF TOMORROW FROM THE HEART DISEASES OF TODAY?

The Thirty-Second Hermann M. Biggs Memorial Lecture

PAUL DUDLEY WHITE

Emeritus Professor of Medicine, Harvard Medical School;
Consultant in Medicine, Massachusetts General Hospital, Boston, Mass.

THE QUESTION

SEVENTEEN years ago on this platform I tried to answer a question asked a generation earlier in 1904 by Hermann Biggs. Today, a half generation later, I would like to pursue this question further. Let me quote first from Biggs himself:

"The terms sanitary science, public or state medicine, and preventive medicine have frequently been used as almost synonymous. The latter term 'preventive medicine', however, (like epidemiology) has sometimes been restricted in its application to the prevention of the infectious diseases. In the broad sense, preventive medicine comprises both general prophylaxis and

* Presented at the Stated Meeting of The New York Academy of Medicine, February 7, 1957. Program arranged by the Committee on Public Health. Manuscript received February, 1957.

individual prophylaxis, and applies to all forms of disease (as does epidemiology), not simply to the infectious diseases. Preventive medicine is an applied science which deals with the preservation of the health, both of the individual and of the community.

"No subject more vitally concerns the welfare of a community than that pertaining to its healthfulness. How the inhabitants live, and how and at what age they die, what is the extent and character of the morbidity occurring among them and what are its causes, are questions of momentous importance. They are essential features in the problem, whose solution will teach men they may live longer, healthier, and therefore happier lives."

Biggs goes on to discuss the prevention of infections but ends with the following observations:

"A very different problem arises in connection with the diseases of the circulatory apparatus and the kidneys. My investigations have shown that in New York City a large increase has taken place, due to these causes, during the last twenty years. The acute respiratory diseases, cancer, and diseases of the circulatory apparatus and the kidneys are the only important causes of death which have shown an increase during this period. The increase in cancer amounts to about 15 per cent, and the increase in acute respiratory diseases to about 15 per cent, while the increase in the diseases of the circulatory apparatus and kidneys combined equals about 40 per cent. In making this statement I have taken fully into consideration the possibility of greater accuracy in the death returns, i.e., the inclusion formerly of these under other causes of death; but after making all allowances, it seems to me without question that an increase equalling 40 per cent has taken place.

"A very important sanitary problem is here presented to the health authorities. What are the factors in the lives of the inhabitants of our large cities (for I have found that similar increases, less extensive, however, have taken place in London, Paris, and Berlin) which have caused such a remarkable increase in the prevalence of these affections, and how are these factors to be removed?"

I concluded my Biggs Lecture of 1940 with the following remarks which immediately followed the quotation just concluded:

> "Thus Biggs already clearly recognized this problem of heart disease as one of preventive medicine and with world wide significance 36 years ago. Can we answer his question? No, I believe not, except in minor details, but we have, I hope, a much clearer conception of the problems left to solve than was possible a generation ago. . . . I feel confident that much progress can be made [and much more rapidly too] during the generation that is to come. . . . *Tempora mutantur, nos et mutamur in illis.*"

Now, half a generation later, how much further have we progressed towards the answer to the question asked by Biggs in 1904? "What are the factors in the lives of the inhabitants of our large cities which have caused such a remarkable increase in the prevalence of cardiovascular affections, and how are these factors to be removed?"

Biggs did not expect one answer for he put his question in the plural, nor can we give one answer that settles the whole problem. However, we can give at least four answers of significance with the most important one, or ones, of all still to be supplied, a most vital challenge to us in the immediate future. Meanwhile, since 1940 we have made great progress in medical science despite the Second World War. Indeed, two of the greatest advances in the control and treatment of cardiovascular diseases actually stemmed from the experience of military medicine, a silver lining to the cloud of war which, however, is infinitely more harmful than helpful in the progress of mankind toward better health and happiness. The first of those two advances was the introduction of the antibiotics which have helped to eradicate the infectious types of heart disease, in particular aortic syphilis, bacterial (malignant) endocarditis, and to an appreciable degree, rheumatic heart disease itself. The second advance was in cardiovascular surgery, a brilliant achievement and still in the early stages of its meteoric career.

Advances have also been registered in diagnostic techniques, more scientific prognosis based on better family histories and more adequate long follow-up studies, and most helpfully of all, in cardiovascular rehabilitation; but the toughest challenges remain in the form of serious hypertension, and arteriosclerosis, not only of the coronary and cerebral arteries but of the aorta itself and of its major branches.

Having thus presented again the question asked by Biggs 53 years

ago and having recognized the major new accomplishments in cardiology since 1940 and the problems that remain, I shall take up one by one the items that can supply partial answers.

In the first place, a great change has taken place in the longevity of the inhabitants of the United States of America, almost wholly dependent on the control of the infectious diseases. Since high blood pressure and arteriosclerosis are much more common in older persons, it is natural to expect more heart disease now. I have recently collected the pertinent data as to age and diagnosis of three groups of 100 consecutive medical patients each, in the wards of the Massachusetts General Hospital 100 years ago in 1856, 50 years ago in 1906 (two years after Biggs' question), and in 1956. One hundred years ago the median age was 27 years and the average 29.9, 50 years ago these ages were 34 and 33.7 respectively, and last year they were 62 and 59.2 respectively. In 1856 over a third of the patients had infections and only three were labelled cardiac, one with pericarditis, one with "cardiac dropsy", and one with "palpitation"; two others had hemiplegia, doubtless hypertensive. There were no cases diagnosed as cancer. One patient aged 45 died from "old age and debility". In 1906 there were 29 with infections and 19 with cardiovascular disease (of which 13 were "rheumatic", 4 had "myocarditis", 1 had cerebral hemorrhage, and 1 had hemiplegia); there was 1 with cancer, and 51 had miscellaneous other diseases or complaints. In 1956 there were 12 with infections, 6 with cancer, and 47 with cardiovascular disease (of which 24 were "coronary"), 12 had hypertension, and 4 were rheumatic. There were 35 with miscellaneous diagnoses.

As somewhat of a check on these clinical analyses I have compared two sets of 100 consecutive postmortem examinations each done at the Massachusetts General Hospital in the 1890's and 1950's respectively (the first autopsies recorded and some of the last). In 1896 and 1897 there were only eleven of the hundred who had cardiovascular disease; 3 with mitral stenosis, 3 with pericarditis, 2 with cardiac hypertrophy and dilatation (probably hypertensive), 1 with bacterial endocarditis and coronary embolism, 1 with cardiac aneurysm and left coronary artery atherosclerosis, and 1 with trauma of brain and heart. There were 10 cases of tuberculosis, 14 cases of pneumonia, 7 of typhoid, 4 of meningitis, 17 of cancer, 1 with sarcomatous metastases in the heart. The ratio of male to female was about 2 to 1 (64 to 36). Only 16 of

the cases were called old, 33 were middle aged, and 43 were young; the age was not noted in the remaining 8.

In 1956 one hundred consecutive autopsies included 51 over the age of 60 in contrast to 16 sixty years before; 30 were middle aged, 13 were young, and in the remaining 6 cases the age was not specified. The males numbered 65 and the females 35, almost exactly the same ratio as in 1896. There were over three times as many cases of heart disease (35 compared to 11) and nearly twice as many with cancer (31 to 17). Infectious diseases were relatively uncommon (12 cases in contrast to 35). Among the 51 cardiovascular cases there were 22 of coronary nature (several also showing the effects of hypertension), 8 with rheumatic valvular disease, and 9 with hypertension, most of which had severe coronary atherosclerosis; 2 showed ruptured aortas, 2 a cor pulmonale, and 1 a congenital defect; 4 had cerebrovascular lesions. Thus here again the age of the cases was apparently the determining factor, in large part at least.

Another very important reason why heart disease is diagnosed more often today is that a good many cases were almost certainly mistaken years ago for something else such as the debility of old age or "acute indigestion", or not discovered at all, or if discovered away from medical centers were not recorded. It is important to remember that the first adequate description of coronary thrombosis was not published until 1912, nearly a decade after Biggs posed his question, and it was not even then widely recognized for still another decade. The pathological description of myocardial infarction and of coronary arteriosclerosis had been, however, in the literature already for many years; in fact the first account of the latter that I can find was entered by Theophile Bonet in the second edition of his *Sepulchretum* of 1700. For some reason or other, despite the good description of pathological cardiovascular conditions, relatively little attention was paid to any clinico-pathological correlation by the practicing physician. Richard Cabot with his famous CPC exercises was a pioneer in calling attention to this need but again that was in the main after Biggs' question. Even when coronary thrombosis began to be diagnosed clinically the milder cases were not included as they would be now. In fact among the 200 cases of coronary thrombosis with myocardial infarction personally seen and collected by myself in the decade between 1920 and 1930 there was not a single mild case; 163 were severe, and the other 37

were "moderate".

Two other types of heart disease were also heavily under-diagnosed: the hypertensive and the congenital.

The blood pressure machine didn't come into common use until a decade or more after 1904 and a good many persons with some but not high degrees of cardiac enlargement from hypertension were missed. It was only when such patients later went into heart failure that they were recognized and labelled Bright's disease or "cardiorenal" disease.

The story about congenital cardiovascular disease is even more interesting still. In the 1920's only one and one-half per cent of several thousand cardiac cases in New England were considered to have congenital defects; twenty-five years later the ratio had increased five fold, with a similar increase in total numbers. Without a shadow of a doubt this did not mirror the true situation. What had happened was that our diagnostic acumen had greatly improved because of our growing knowledge of the frequency of these defects, because of new diagnostic techniques, and also because children with congenital cardiovascular disease were finally being brought by their family doctors and parents to consultants and clinics in the larger medical centers since, at last, surgical treatment to help them had been developed.

A third reason for the increase in the diagnosis of heart disease of late years has been a change in the fashions of nomenclature and statistical analysis. What used to be called death from old age or debility, even at 45, was often a cardiovascular death, perhaps from coronary insufficiency or pulmonary embolism or aortic rupture or a cerebral vascular accident. Now all these are included under the category of cardiovascular disease. And arteriosclerotic disease of the kidneys, which we have found to be one of the chief hazards of extreme old age, has now rightly been shifted from primary kidney disease to where it belongs. One doesn't die from "old age" alone.

And finally, in the course of this change in diagnostic customs, many deaths that are sudden or rapid in their course are labelled as of coronary origin even without autopsy confirmation. With little doubt most of these cases are correctly designated but an unknown number are not, as noted by Dr. Lew a few weeks ago at a meeting of the New York Heart Association here in New York City.

Having presented these four reasons for at least some of the increase of patients diagnosed as having heart disease we are left with the likeli-

hood of an actual increase in young and middle-aged men in the form of coronary thrombosis. It is the challenge of this leading heart problem which demands our greatest efforts. Regardless of what its evolution has been—it has descended upon us in epidemic proportions. Coronary thrombosis is not simply a problem of atherosclerotic disease of the coronary artery wall; it involves the blood clot too and the greater tendency for the blood to clot in some individuals than in others. And the arterial wall lesion is not such a simple matter either. More than a deposition of cholesterol fat droplets is involved. Patterson's finding of the frequency of intramural hemorrhages, now being confirmed by Helpern and Weinberg, and Texon's thesis of a possible or indeed probable physical or mechanical, that is, primary hydrodynamic factor in initiating the whole process are in great need of further study. We are in the midst of a fascinating wide-open future in pathological as well as in epidemiological relationships.

The Answer

And now, after these introductory observations, let us turn to an attempt to answer Hermann Biggs' question posed 53 years ago. Although experiments on animals of all kinds have afforded considerable information of value regarding the factors causing the various kinds of heart disease in man, their application to human disease has in the main been inadequate because the various kinds of heart trouble in man occur infrequently, if ever, spontaneously in animals. Partial duplication can be induced with difficulty in some species but is a very poor substitute for the real thing in man. This is true of practically all varieties that have been studied, whether in fowl, mice, rats, cats, dogs, or monkeys.

Man himself has been studied experimentally as to exposure to various factors such as diet, exercise, stress, and relaxation, but these studies, although worth while, especially because one factor at a time can be altered, have usually been too brief or too limited in severity to yield the most important information. And so quite naturally one turns to nature's experiments on man, done on a grander scale over generations or more of time, and often in intensive degrees. Valuable information of this sort is to be obtained by comparing one population with another living under the same conditions but best of all by comparing various groups of the same population living under different

conditions. Such an epidemiological study, fascinating and vital as it is, must be acknowledged to be complicated, difficult, and expensive. When I discussed it in 1940 it was practically non-existent but it looked well on paper.

In presenting my hopes at that time in my first Biggs Lecture I wrote as follows:

> "Heart disease is a world problem, as much as is tuberculosis or dysentery or influenza but it has not yet been investigated as such, in contrast to many of the infectious diseases which have scourged the world, especially in the form of waves of devastating epidemics. It is natural that the rapidly fatal and highly contagious diseases should be studied first and brought soonest under control, leaving for us of the present day the study and control of the less dramatic, more insidious and gradual but no less fatal maladies such as heart disease and cancer. International cooperation and world wide study have become the matter of fact procedure in dealing with the serious infections. The pioneer work of the Rockefeller Foundation and other groups transcending national boundaries have broken the ground and shown the way. It should not be too hard to follow their footsteps in the collection of invaluable information about the most important causes of heart disease and the incidence and severity of their effects on the heart *under all sorts of conditions and in every corner of the globe*. Nature has for centuries been conducting gigantic experiments as to the effect of climate, of type of work, of diet, and of local or world wide disease on men, women, and children of different races, that are spread out before our very eyes for us to record and to analyze, more readily yielding information than might ever be obtainable by our own experiments on man, although certain tests could be added to enrich the findings. Under the most exacting conditions animal experiments of this sort cannot be completely applied to man; important clues and discoveries can result from experiments on laboratory animals, but if we rely only on them we are letting go to waste an equally important source of information about heart disease.
>
> "Statistics from surveys are slowly accumulating in this country and in certain other countries but by different uncorrelated groups, making them often difficult or even impossible

> for direct comparison. We need a large well organized study that can in a several-year program collect information that will really show how common are hypertension and rheumatic valvular disease and syphilitic aortitis and coronary artery disease in relation to climate and mode of life. Several well and similarly trained groups armed with good clinical observers, stethoscopes, sphygmomanometers, electrocardiographs, x-ray apparatus, and autopsy technic could in a few years accomplish more than the next century of desultory work and cost less than a single air raid over a city at war. Can't we divert the energy going to waste in destruction to these interesting and constructive efforts for humanity throughout the world? At least let us raise our voices in this direction just as soon as they can be heard, and in fact there is no reason why in this hemisphere we may not get started in this work within the near future if some group or individual will heed the call to finance the first expedition."

Our participation in the Second World War began shortly after this appeal and prevented any full scale studies although circumstances did present data of value, as in the case of the Scandinavian countries during and after the Nazi occupation. Finally, in the last few years concerted efforts, sparked by Ancel Keys, Fredrick Stare and a few other vital pioneers, have begun to scratch the surface. And at last the growing realization of the importance of such epidemiological research has attracted the attention of those formerly trained in the epidemiology of infectious diseases and in public health. At last there is beginning to grow up a concerted effort to dig more deeply, through the cooperation of physiologists, biochemists, clinical cardiologists, biostatisticians and public health workers trained in the field of the epidemiology of infectious disease. This research, which still requires much more support, both moral and material, than it has had in the past, has expanded to cover the globe and is enlisting scientific workers from many different countries.

Epidemiological Research

In the remainder of my time I would like to present the problems that must be met in the effort to provide the final answers and the scant information already available about two of the greatest public health hazards of all, which happen to involve the heart and the blood vessels,

namely hypertension and coronary atherosclerosis. They may be considered together, but with certain distinctions since they are separate diseases.

We hear and read a great deal today in both medical and lay circles about the effects of stress and strain, of diet, and of exercise on the heart and blood vessels, but we have as yet very little sound information based on accurate and adequate study. The surface has barely been scratched. Before I discuss what we know and especially what we must yet learn about those environmental factors let me present to you the basic factors which concern the person himself in the causation of heart disease. In my Biggs Lecture of 1940 I took up one by one the different kinds of heart disease but I had little to say about the host. Although at that time I used in my discussions about the causes of heart disease a companion title, namely, "The Ways of Life and Heart Disease" comparable to the heading of my 1940 Biggs Lecture, namely, "Heart Disease—A World Problem", I did not take adequately into consideration the total epidemiological picture which, of course, includes the host or the person himself equally with the agent or the disease process. For some years now I have appreciated the great importance of the host, ranking at least as high as, if not indeed higher than, that of the agent. Hence, I shall now present what I like to call the basic factors which concern the host and which in the present world status have been and still are largely beyond our control and which easily explain the fatalism of past generations to which I shall return shortly.

The Basic Factors Which Concern the "Host"

We know what most of these basic factors are, but not necessarily all of them. Therefore let us save space for an X-factor or two which may be discovered in the future.

Race may be considered first. It is quite possible that there are racial differences in reactions to environmental factors like stress and strain and diet and exercise, as there are known differences in response to exposure to various infectious diseases. When I was in France with the A.E.F. during the First World War, we had temporarily under our wing at our base hospital a number of French African soldiers sick with the measles. Their mortality rate was high due to their almost total lack of immunity to the disease. And so it may be in some instances with respect to hypertension and coronary heart disease. Most

of the initial studies that have been carried out, however, suggest that racial responses to stress and strain and to diet are very similar and that in this relationship the environmental factors are predominant. However, much more research in the field itself, both intensive and extensive, will be needed to obtain the correct answer to this important question.

Heredity comes next. Here we know from the personal experience of hundreds of thousands of practicing physicians throughout the world that inheritance of susceptibilities to disease, including important degrees of hypertension and coronary atherosclerosis, and resistance thereto, are of very great importance, perhaps more important than any other factor, whether basic or environmental. But just how heredity acts and whether there is any way to alter such an effect remains for the future to determine. We have done almost nothing about this problem as yet, partly because of its difficulty, partly because we have not appreciated its importance, and partly because there are as yet very few well trained human-geneticists in the country or in the entire world today. Here is a challenge of the greatest magnitude.

Some of the results of heredity have been correlated, in partial degree at least, with coronary heart disease in young adults. Although the most striking of all clues in studies that we have carried out concerning such young candidates is that of sex, there are other findings largely dependent on heredity that have been prominent. One of these is body build. In anthropological studies conducted a few years ago by a number of us in Boston, mesomorphy, that is a broad muscular build, figured prominently in our young coronary cases. There were no predominant ectomorphs in the entire series of 100 cases and there were only a few predominant endomorphs. There were quite a few endomorphic mesomorphs and still fewer ectomorphic mesomorphs but mesomorphy of high degree was frequent. Just how this is related directly, if at all, is obscure.

Another inherited feature in young cases is hypercholesterolemia. Coronary heart disease has certainly been found more commonly in individuals and families with very high levels of serum cholesterol. It has also been stated on occasion that there are personality characteristics but a great difficulty in such studies has been that they have been conducted after a myocardial infarction rather than before and not infrequently a change has been observed resulting from the illness

itself. It does seem true, however, that a predominant mesomorphy tends to have an energetic, impatient personality often tending to drive himself and others too, but it is not necessarily the drive which may produce stress and strain but other characteristics of the individual who happens to have this drive that very likely are responsible. The same may be true in such an individual with respect to an excessive use of tobacco or alcohol.

Age. Autopsy studies in successive decades after the age of 50 have shown increasing frequency of coronary atherosclerotic individuals and often with increasing degree of severity, although this does not always hold true. Clinically, however, it is in the fifties and sixties that the majority of the patients come to us with coronary heart disease and the same is true of hypertension. By the time of the seventies or eighties a good many have succumbed which may in part account for the smaller numbers. Another reason why the problem tends to decrease with the oldest ages is that as a person gets much older and retires, he is much less active and is under much less strain, physical and emotional. Perhaps one of the most interesting aspects of the relationship of age to coronary heart disease is the natural tendency for recovery partly through the natural development of an adequate collateral coronary circulation in many persons, partly because of the good healing tendency in most instances of acute myocardial infarction, and partly because the individual himself or herself decreases his activity to suit his reserve. This applies somewhat to hypertension too.

Sex. Sex plays a major role as a basic factor not only in coronary heart disease in younger individuals but also in the severity of hypertension in middle age. The male sex has the higher degree of involvement in both cases. After the menopause, however, the female is no longer protected from serious coronary atherosclerosis and may be involved. It is now well known that the female hormone protects the male in many species of animals including man. A note of a recent study by the Oklahoma Medical Research Foundation reports the serum lipids, lipoproteins, etc., in eunuchs and non-castrated institutionalized male subjects, stating that the serum lipid pattern which distinguishes the eunuch from the non-castrate may be importantly related to the eunuch's relative freedom from significant coronary atherosclerosis. Much research is still needed in the effort to discover some fraction of the female hormone or similar chemical agent that may be

protective without feminizing.

Thus, a review of these basic factors concerning the host helps to explain the attitude of fatalism and of pessimism about progress in medicine that was held over the centuries doubtless from the time of the beginning of recorded history. During this long period little was known or done about the agent, whether infectious or non-infectious. About 200 B. C. the Preacher in Ecclesiastes expressed the attitude which held sway for well over 2000 years and as a matter of fact was still largely in force at the beginning of my own medical career. I would like to quote a few verses from the 1st and 2nd Chapters of Ecclesiastes:

Chapter 1

2. "Vanity of vanities, saith the Preacher, vanity of vanities; all is vanity."
3. "What profit hath a man of all his labour which he taketh under the sun?"
4. "One generation passeth away, and another generation cometh: but the earth abideth for ever. . . ."
9. "The thing that hath been, it is that which shall be: and that which is done is that which shall be done: and there is no new thing under the sun."
10. "Is there any thing whereof it may be said, See, this is new? it hath been already of old time, which was before us. . . ."
14. "I have seen all the works that are done under the sun; and, behold, all is vanity and vexation of spirit."
15. "That which is crooked cannot be made straight; and that which is wanting cannot be numbered. . . ."
18. "For in much wisdom is much grief; and he that increaseth knowledge increaseth sorrow."

Chapter 2

11. "Then I looked on all the works that my hands had wrought, and on the labour that I had laboured to do: and, behold, all was vanity and vexation of spirit, and there was no profit under the sun."

Only during the last generation or a little more have we been able to turn from such a spirit and life of fatalism and pessimism to the optimism that abounds in medicine today. This change has come largely through a change in environment. Man has made crooked things

straight, has cured defects surgically within the heart and blood vessels. Man has used potent medicines effectively and now we believe that he may, through other alterations of the environment, succeed in protecting the young candidates of the future against these serious diseases of today especially so far as the heart and blood vessels are concerned, namely hypertension and coronary heart disease.

Environmental Factors, Which Are "The Agent"

It is the environmental factors in particular to which Hermann Biggs and I referred in 1904 and 1940 respectively and it is concerning these that we may look hopefully to the results of research. What are these factors? We can name some but space should be reserved for others not yet identified or specified which we may call Y and Z.

Stress and Strain. The first that is so much discussed nowadays and which undoubtedly plays a role at least in a secondary, precipitating, or aggravating capacity is stress and strain. By this we mean primarily emotional stress. Physical and mental strain are sometimes included, but should be considered separately primarily as work or exercise. It has long been recognized that the emotions, by influencing the psyche, have a great deal to do with health. In fact, until the last generation or two, the only medicine that could really be practiced, except for a very few specific remedies, was psychosomatic medicine. This still is an important part of the work of the physician but it has not been adequately studied. That the emotions can alter the physical, chemical, and physiological aspects of the body is quite certain but the mechanism is still obscure and could be well and profitably investigated. However, to blame stress and strain for such diseases as coronary heart disease or even hypertension is still premature. It has been the experience of people through the ages and of many of us today that stress and strain are universal and probably have existed in high degree all through history. This generation has no monopoly on stress and strain. Every generation has complained of its emotional difficulties and it isn't just a matter of the speed of modern life. There was probably more stress felt by some person in the Middle Ages running to escape some dire fate than we ourselves may encounter sitting comfortably in an airplane, as I did this morning, travelling 400 miles an hour.

There are, however, five considerations concerning stress and strain that need special comment. Without doubt, one is that in the presence

of important degrees of high blood pressure or of coronary atherosclerosis with impending insufficiency, emotional stress and strain can aggravate the condition, precipitating trouble and even causing sudden death when the reserve is very low. The second consideration is that what is stress or strain for one individual may not be for another. Here the host, of course, must be considered as well as the agent. A third consideration is that a certain amount of stress and strain may actually be helpful in the maintenance of a state of vigorous health. The fourth consideration is that it is quite possible that repeated stress and strain over long intervals of time may in certain individuals establish higher levels of blood pressure and indeed even changes in the blood vessels, to which I shall refer next. Finally, an interesting new clinical viewpoint about the beginning of atherosclerosis, already referred to above, is that hydrodynamic strain which may be increased by emotional stress with increase in blood flow and blood pressure may act to initiate and to aggravate the earliest lesions of the intima of blood vessels, such as the coronary and cerebral arteries and of the aorta and its main branches. I would like to refer to a measure that I have used in the treatment of patients who are subjected to stress and strain or who worry very much about themselves or others. This is the form of a prescription which I write for them. Instead of a medicine, I not infrequently prescribe the reading of Sir William Osler's *Aequanimitas*, the delightful essay which he gave as the valedictory address at the University of Pennsylvania in 1889. I can recommend it highly to all to read even though it was addressed primarily to the medical students and the medical faculty.

Research on the effect of stress and strain on the heart and circulation is badly needed and must be carried out despite its complexity and difficulty. One of the committees of the American Heart Association which has been asked to submit recommendations concerning the effect of strain and trauma of the heart is laboring with this problem at present and has been doing so for several years. Eventually we hope that there may be some useful recommendations resulting from researches now going on.

Exercise. Our medical ancestors were obliged to exercise much more than is the custom of most inhabitants of the so-called more civilized countries of today. Prosperity has brought with it great neglect of this health measure and in one generation there has been a very striking

decrease in the use of our muscles. Although we have no adequate proof yet that such neglect is very harmful and although it is doubtless possible to live long and exercise little, there is a difference between a state of positive health favored by exercise and that of a soft physical condition even in the absence of disease. Exercise has physiological benefits and improves the circulation, in fact it acts as an accessory pumping mechanism to help the heart. Good muscle tone in the extremities compresses the veins which with well acting valves help to return blood to the heart. Free motion of the diaphragm favored by vigorous exercise helps not only to bring air into the lungs but, through its negative pressure as a pump, helps to bring blood up from the lower part of the body back to the heart.

In addition, exercise, without any doubt, has a favorable effect in most individuals as at least a partial antidote for nervous stress and strain. It so acts with me and many of my friends and patients. The President himself obtains great benefit through the relaxation of nervous tension which comes with his exercise. Doubtless the more highly muscled individuals need more exercise, and when we think of the common practice of our ancestors only a generation or two ago of walking long distances routinely, of helping to clear the forests, and of vigorous hunting and fishing, we must admit that our present way of life is very different. I would like to quote a stanza written as part of a letter by John Dryden in 1680 extolling the advantages of the country life and exercise. It is, of course, a rather extreme viewpoint but I believe that there is more truth than poetry in it.

"By chase our long-liv'd fathers earn'd their food;
Toil strung the nerves and purified the blood;
But we, their sons, a pamper'd race of men,
Are dwindled down to threescore years and ten
"Better to hunt in fields for health unbought
Than fee the doctor for a nauseous draught,
The wise for cure on exercise depend;
God never made his work for man to mend."

Finally, with respect to exercise, there is the possibility that it may have a favorable effect in retarding the onset of coronary heart disease. Some suggestion of this comes from experimentation in animals and in man too, but much more research is needed before we can speak with any certainty one way or the other. I myself have found that exercise

in moderation is one of the best ways to treat many of my convalescent cardiac patients. The establishment of a good program of regular exercise, I find, is often more important than many medicines.

Diet. The particular way of life or environmental factor that has attracted the most attention in the epidemiological studies that have been going on in the last few years has been that of diet. Unfortunately, premature advice based on inadequate evidence has become the fashion. but we must await further detailed studies during the next few years before we can be sure of the best advice to give either to healthy persons to prevent trouble or to those who already have high blood pressure or coronary heart disease.

Salt. We do know that hypertension tends to be aggravated by a high intake of sodium and hence diets low in sodium, represented ordinarily by common salt, have been found useful. It is rarely necessary, however, to decrease the amount of sodium to such a low level as that in the famous rice diet of Dr. Kempner. There is no doubt that remarkable gains have not infrequently been secured by such rigidity of diet, but on the other hand, it has not been necessary in many cases to go to such an extreme. So far as the coronary circulation is concerned, in the absence of congestion or hypertension, a low sodium intake does not seem indicated.

Further consideration of salt in the diet brings up the possibility of a causative relationship between unusually high salt intake, such as that which is found in some parts of Japan, and hypertension which is quite common there even when coronary heart disease is uncommon. Further studies of this interesting possibility are advisable.

Fat. The most interesting dietetic problem of all concerns the fat intake. For a long time, at least as far back as 25 years ago, a diet rich in fat has been incriminated as a probable cause of coronary heart disease. I myself can well remember the days when Timothy Leary and Elliott Joslin of Boston independently gave some of us advice not to eat two eggs for breakfast because of their high cholesterol content and this advice has since then been strengthened by a much wider circle of investigators and their followers. However, the questions and answers are more complicated than that. In the course of the last decade, viewpoints have changed a good deal and because of this there are a good many skeptics. I suppose that the truth rests somewhere between the viewpoints of those individuals who are vigorous in their advice to

beware of all fats and those who go to the opposite extreme in their advice to pay little or no attention to the fat content of diets or even to advocate high contents of fat as does the explorer, Stefansson.

Studies initiated by Ancel Keys, in some of which I myself have participated, have shown that in different parts of the world particularly in Italy, South Africa, Japan, Hawaii, Sweden, Finland, and the United States those populations exposed to a rich fat diet appear to be afflicted by much more coronary heart disease than populations not so exposed, no matter what other factors there may be. However, this is all in the form of preliminary studies and much more research on total populations themselves is needed for fuller appraisal.

First of all, historically, I suppose obesity in general was considered an important error which might lead to coronary heart disease no matter what food supplied the excess calories inasmuch as the body can manufacture its own fat out of carbohydrate and protein. Then the pendulum began to swing somewhat away from that point of view and incrimination began of all the fats responsible for the increased calories, that is, both animal and vegetable fats, and that this might happen even without obesity. Also at this time it began to be widely recognized that it was not necessarily the increased work demanded by carrying around extra weight but the fact that a few ounces of fat in the wrong place, in the coronary walls for example, might do more harm than many pounds of fat simply under the skin. The next change came when a sharp distinction was made between animal fats and vegetable fats, the former being considered hazardous and the latter safe, no matter what kind of animal or vegetable fat. The next change has been much more recent, with an indication that hydrogenated, saturated, or processed fats, whether animal or vegetable, were likely to be the villains in the piece rather than the unsaturated, non-hydrogenated, or unprocessed fats.

Finally, the latest information of all suggests that some protection is afforded by certain fats of the same chemical nature represented particularly by corn oil and certain fish oils, and somewhat less by cottonseed oil (in contrast to cocoanut oil which seems to be in the same class with some of the animal fats). However, conversation a few days ago with Ancel Keys indicates that the protection afforded by corn oil is slight or nil when it is simply added to the ordinary diet, which has the additional disadvantage of increasing the calories.

If other fats are replaced by corn oil or fats of similar chemical constitution there seems to be a "favorable effect" on the serum cholesterol content, which may or may not be reflected in protection of the coronary wall from atherosclerosis.

Thus it is quite obvious that we are in the midst of the evolution of much important research and that no hard and fast statement can yet be made about diet. All we can advise at present is to avoid both obesity and an over-rich fat diet—probably a fat content not exceeding 25 to 30 per cent of the total calories is quite reasonable. This too may be partly dependent on the amount of regular and vigorous exercise.

Tobacco and Alcohol. Too little is known accurately about the effect of tobacco and alcohol in the production of the atherosclerotic process but there seems to be little or no likelihood that these are involved in the underlying process. However, given severe atherosclerotic changes with coronary insufficiency or an important degree of hypertension, tobacco and even on occasion the overuse of alcohol can be very harmful because of the aggravation of the disease process.

Conclusions. In summary then it may be concluded from the observations that I have made in this lecture that we are not yet on solid ground with respect to advice that we may give to the youth of tomorrow to avoid certain of the heart diseases of today, especially hypertension and severe coronary atherosclerosis. We may need another decade or two before we can speak with assurance. Perhaps the best advice is to carry out common sense measures that lead to a state of positive health and to support in full the important research of all possible causative factors that is in progress today and which will be developed more fully in the future.

In the last analysis our goal is not to advise one single program of ways of life, i.e., environmental factors, for everyone, but to take cognizance also of the basic factors which concern the person, i.e., the host himself. We must fit the advice to the particular needs, and especially to protect the candidates from serious hypertension and coronary heart disease in youth and middle age. This goal therefore demands intensive research in heredity and other basic factors since they are at least as important as environmental factors acting as the agent. Thus the challenge is twofold.

PRESENT STATUS OF THE FULL-TIME SYSTEM*

JOSEPH C. HINSEY, Ph.D.

Director, The New York Hospital-Cornell Medical Center

DURING the year 1955-56, there were 76 fully approved four-year schools and six approved schools of basic medical science. There are 11 approved four-year medical schools in Canada, one approved school of basic medical sciences and one newly developing four-year school. The following new school developments should be noted:

1) The Albert Einstein Medical School in New York admitted its first class in September, 1955. 2) The University of Florida at Gainesville, and Seton Hall College of Medicine in Jersey City, N. J., admitted their first classes in September, 1956. 3) The University of Missouri at Columbia, Missouri, and the University of Mississippi, at Jacksonville, Mississippi, extended into the third year in September, 1955 and will graduate classes in 1957. 4) The University of Kentucky has been authorized to establish a four-year medical school at Lexington. 5) There is consideration being given on several other university campuses to establish a medical school.

In discussing the present status of the full-time system, I shall refer only to the schools in this country. The improvement in medical education which followed the report of Dr. Abraham Flexner[1] in 1910 was largely due to the assumption on the part of our American Universities of responsibility for the programs in their medical schools and the establishment of the university tradition in the educational philosophies of our schools. During this time another extremely important factor which has brought about the much improved level of teaching, research and patient care has been the full-time system which has been prevalent in our medical schools. Deitrick and Berson[2] make the following statement:

> "At the turn of the century many forces were brought to bear upon medical schools to establish adequate laboratories for the teaching of the

* Presented at a meeting of the Section on Historical and Cultural Medicine at The New York Academy of Medicine, January 23, 1957, as part of a symposium on *The Future of Medical Education*. Manuscript reviewed January, 1957.

sciences and for the employment of full-time faculty members in these departments. Flexner described the 'wretched' laboratories found in a majority of the medical schools in 1910. The clinical departments were staffed almost entirely by volunteers or a few part-time faculty members. Of the 155 medical schools he surveyed, Flexner mentioned only 14 or 15 with any laboratory facilities definitely designated for the clinical departments. Of the schools mentioned, often only one clinical laboratory existed for the use of all the clinical departments. Within a period of 40 years since Flexner's report, not only have laboratories been provided for medical basic science departments, but there has been a very rapid development in the appointment of full-time or geographic full-time men in the clinical departments and in the establishment of research laboratories for their work, so that clinical research has become a common term."

Professor Donald Fleming[3] of Brown University has published an article: *The "Full-Time" Controversy*. He described the key figures in this controversy as William H. Welch, Franklin P. Mall and William Osler. It was extremely interesting to me that it was while Mall was working with Ludwig in Leipzig during the winter of 1885-86 that Ludwig, then an old man, confided to Mall that he had a dream of placing clinical medicine on a University basis with clinical professors, as well as preclinical, devoting their full time to research rather than engaging in private practice on the side. Mall was so impressed with this that he became a protagonist of the full-time system and strongly interested Lewellys F. Barker who for a time succeeded Mall as the Professor of Anatomy at the University of Chicago and it was in 1902 that he addressed the western alumni of Johns Hopkins in Chicago and came out for clinical full-time. This address attracted great attention throughout the country according to Fleming. In spite of Osler's strong opposition, it was in 1913 that Welch announced to the General Education Board that Johns Hopkins would institute a full-time system in the clinical departments. The Board then appropriated $1,500,000 to implement it. I regret that time does not permit a more complete discussion of Fleming's most interesting paper. However, he concludes his article by saying: "From 1913 forward to 1939 the principal objections to full-time for the leading men in clinical departments grew increasingly faint; and all progressive schools gravitated toward full-time."

A corps of full-time clinical staff members is a necessity in our modern medical schools because of the increased demands made by the clerkships for undergraduate students, the large amount and intensification of the undergraduate teaching in the clinical fields, the development

of out-patient teaching for better teaching at all levels, the residency programs, medical research projects, and greater participation in community activities at all levels—international, national and local. At first endowments were provided to cover the salaries of the full-time men, but even from the beginning some of these full-time men did limited amounts of private practice. As time has gone on, few of our schools have had the means to provide full-time salaries for all of the necessary full-time people needed in the clinical fields, so that various plans have developed for the financial remuneration of clinical faculty depending upon the amounts of private practice. I have been impressed by the contributions made by the part-time and volunteer faculty members. They serve an important function in community relations and in those with the outside profession, as well as what they do in teaching, research and service. However in general it may be said that they contribute most effectively in departments where there is full-time leadership. In my opinion, a proper balance between part-time and full-time staff is important for the effective functioning of a clinical department.

At the meeting of the Association of American Medical Colleges in 1955, a symposium was held on the compensation of clinical faculties and in the July 1956 issue of the *Journal of Medical Education*, this symposium is reported with the exception that the paper delivered by Dr. George Packer Berry, Dean of the Harvard Medical School, on "The Harvard University Plan" which was presented at Swampscott, Mass., was not included in the published report. However, in these reports, Dr. Lowell T. Coggeshall has described the University of Chicago Plan for Medical Education. Today it would be called a strictly full-time plan. He summarized by stating that it includes three basic principles: 1) a complete full-time staff of true university status, 2) practically the complete utilization of paying patients for medical education and 3) the encompassment of the medical school within a university life science group. Dr. Wilburt C. Davidson, Dean at Duke University Medical School, described the "Duke Private Diagnostic Clinic". In this institution, the strictly full-time faculty receive salaries comparable to those of equal grades in similar institutions and includes all the members of the departments of anatomy, biochemistry, physiology, pharmacology, pathology, bacteriology, preventive medicine, radiology, anesthesiology, administration, nursing and dietetics, and one third of the faculty in medicine, neuropsychiatry, obstetrics, pediatrics

and surgery. The members of the geographic full-time staff are paid smaller salaries but they share in the income derived from the private patients in their respective fields collected through the private diagnostic clinic. Dr. Thomas Hunter, Dean of the University of Virginia and Dr. Norman B. Nelson, Dean of the University of Iowa Medical School, outlined plans which have been developed in their institutions where members of their geographic full-time staff carry on private practice and share in the fees according to a plan developed in each of their institutions. At Harvard University, Dean Berry stated the plan there makes it possible for any member of the Harvard faculty, whether it be in the medical school or in other divisions of the university, to do outside professional work in a total amount equaling the basic university salary. This has come to be known as the "Harvard Plan" or the "Harvard Matching Plan". In other medical schools various arrangements have evolved which make possible supplementation of faculty salaries from fees collected by them from patients under their care.

In February of last year I[4] presented the problems which deans and medical administrators in general face in maintaining the full-time clinical faculty. This problem of recruiting, maintaining and compensating the staffs of our medical schools and teaching institutions is a difficult one. Inasmuch as the staff members of these institutions participate also in educational programs of the allied health professions, what we are considering is of vital importance to the maintenance of the nation's health. The administration of a teaching institution is concerned not only with the staffing of our clinical departments but is also faced with a perplexing problem related to the teachers in the basic medical sciences. With the limited resources at his command, the medical college dean is sometimes forced to the consideration of complete abandonment of the full-time system and the return to a system of medical college staffing used at the beginning of the century, a system that would set medical education back in a harmful fashion. As a matter of fact, the full-time system as envisioned by Abraham Flexner in 1910 is just struggling along in many of our institutions. Many of our difficulties would be ironed out if we had a great deal more money, more than seems available at the present time. However, while these problems are complex and difficult they must be faced with fairness and equanimity. The medical profession has much to gain if our program of medical education remains vigorous and strong and it has much to lose if our medical

schools are weakened. All of us are in this together and we must work it out in such a manner that the teaching of our future physicians and members of the allied health professions is maintained at a high level and is advanced whenever possible. The medical school administrations must see to it that they do not compete unfairly with the practicing profession and, by the same token, the profession should recognize the needs of our medical schools. We should not confuse our code of medical ethics with medical economics; the medical schools must not exploit any members of their staffs, and in turn, staff members must not exploit the institutions to which they belong. At the beginning of the installation of the full-time system in many of our teaching institutions there have been differences of opinion between the practicing profession and the members of the medical school staffs. This has led to misunderstanding on both sides and recriminations that have been harmful to all of medicine. As time goes on and the institutions' programs evolve and develop, almost invariably the value of the full-time system has come to be appreciated by the whole medical community.

I now wish to relate what has transpired at a national level in the action of the American Medical Association. Because of problems arising in the development of the four-year medical school program at the University of Mississippi at Jackson, Mississippi, Dr. J. P. Culpepper, Jr., a member of the House of Delegates of the A.M.A. introduced a resolution on medical practice by medical schools at its meeting in December, 1954. This resolution reads as follows:

> "WHEREAS, It is imperative that a climate of free enterprise and ethical, private professional practice prevail toward the end of providing all Americans with the best possible medical care; and
>
> "WHEREAS, Corporate, and tax-subsidized practice manifestly defeats these ends of service; and
>
> "WHEREAS, There patently exists a barrier to these ends in the device of a tax-supported medical school that is engaged in the practice of medicine in which fees are levied and collected under a policy allowing this practice to employed physicians; now therefore be it
>
> "RESOLVED, That the American Medical Association reaffirm its unalterable opposition to socialized and state subsidized medicine regardless of the form that it may assume; and be it further
>
> "RESOLVED, That the House of Delegates of the American Medical Association is of the opinion that these principles should be considered by constituent and component medical societies together with all other facts pertinent to the local situation in all controversies arising in the employment of the medical faculty by state (tax) supported medical schools and be fully considered in effecting action within the framework of this policy."

It was surprising to many of us that this resolution was not referred to the Council on Medical Education and Hospitals of the American Medical Association. However, it was referred to the Council on Medical Service which proceeded to make a study of the methods used in compensating the clinical faculties. This Council chose representatives of the Association of American Medical Colleges and from the Council on Medical Education and Hospitals of the American Medical Association, as well as from the American Hospital Association to serve as an advisory committee to them. However, the experience of the medical college representatives was that advice was sought comparatively little and they participated in a minimal amount in the establishment of the final policy. Questionnaires were sent to state medical associations and the county medical societies in areas where medical schools were located. In addition, questionnaires were sent to the medical schools over the country. Seventy-two medical schools were involved in the report which was made of this study. Fifty reports were received from state medical associations, about 54 from medical schools and there were 47 replies from county medical societies. It was interesting that this committee envisioned the function of modern medical schools to be—a) to educate future physicians; b) to educate other medical personnel; c) to conduct research for the advancement of medical education and d) to render such medical services as are necessary to accomplish a, b and c above.

The word full-time has come to have a number of meanings and we should bear in mind the definitions that accompanied the questionnaire which was sent out by the Council on Medical Service of the American Medical Association. This questionnaire, by the way, contained 13 major questions with subdivisions and dealt with the numbers, ranks, types of practice and methods of compensating medical school faculties.

A. An Absolute Full-Time faculty member has as his primary responsibility teaching and research activities in the Medical School and in its clinical facilities. His total income from professional activities is derived from the University and related sources. He may see and render care to pay patients only within the medical school and its clinical facilities, but his personal financial compensation from the medical school is fixed without reference to such service. (It should be emphasized that he is

not permitted to keep these fees. They are used by the university to support medical education and research.)

B. A Geographic Full-Time member has as his primary responsibility teaching and research activities in the Medical School and in its clinical facilities. He receives a salary from the University and possibly from related sources, but he also has the privilege of receiving personal financial compensation for services rendered to pay patients, which he can care for in the clinical facilities of the medical school.

1) Geographic Full-Time, Unrestricted: No specific limit is placed (other than in keeping with the primary responsibility mentioned above) on amount of income derived from and/or time devoted to services to pay patients.

2) Geographic Full-Time, Restricted: A specific limit (over and above that related to the primary responsibility for teaching and research) is imposed by the University as to the amount of income that may be derived from and/or the time devoted to services to pay patients.

C. A Part-Time faculty member is a practicing physician who desires to devote part of his time to teaching and research in the Medical School and its clinical facilities, for which he receives a nominal stipend. He maintains his own facilities for medical practice and he is in no way responsible to the University in regard to where he sees pay patients, how many such patients are seen, nor how much income is earned.

D. A Volunteer faculty member is the same as a part-time faculty member except that, because of local tradition and/or amount of time and degree of responsibility involved, he receives no stipend from the University.

This report contains much interesting information but we shall have to limit the amount of consideration of the material here.

Sixty-five per cent of government supported schools have absolute full-time faculty and 91 per cent have geographic full-time faculty. Of the private schools, 90 per cent of the schools have absolute full-time faculty and 84 per cent have geographic full-time faculty. Ninety-seven per cent of the schools, including both government and privately

supported schools, reported that Deans believe that salary implementation from fees from private practice is necessary in varying degrees to permit them to attract and retain competent full-time teachers. It was interesting that in the replies from the medical societies, a majority of the state associations and the county societies believe that it is necessary to have faculty members engage in private practice to improve the teaching by contact with private patients and to augment their income. To quote from their report: "While a majority of the Medical Association and County Society replies indicate a need for such private practice, a perusal of the comments would indicate that the majority of those reporting feel that the ideal would be for the so-called 'full-time' teachers to be on a strict full-time basis with private practice limited to consultation or occasional referred cases. However, many indicate that they believe private patients are necessary for a sufficient supply of clinical material and to provide an opportunity for a different type of teaching. In general, it may be said that the supplementation of income by private practice seems to be condoned as necessary in situations where governing bodies do not pay sufficient salaries to attract highly trained clinical men."

Without giving the medical schools and the universities an opportunity to consider the conclusions and recommendations made by the Council on Medical Service, the House of Delegates of the American Medical Association adopted a report of this Council entitled: "Private Practice by Medical School Faculty Members" in June, 1956. This report contained a recommendation that all patients, treated in medical school facilities, be available for teaching purposes. As far as the full-time faculty is concerned, this statement is made:

"It is the Council's *belief* that a nucleus of 'full-time' clinical faculty members in the medical school is necessary. The Council *believes* that as a general rule the 'full-time' clinical faculty members, as herein defined, should *not* be permitted private practice but should be paid an adequate salary by the medical school. Exceptions because of legal or local conditions may be necessary. The number and types of such 'full-time' faculty members as are deemed necessary rest with each school, but in any event their salaries should be adequate and attractive enough to hold capable teachers."

In regard to the practice of the geographic full-time group, the recommendations stated that: "The Council *believes* it is a primary responsi-

bility of the administrators of medical schools to exercise adequate control over the extent of private practice so as to maintain a proper relationship between teaching responsibilities and private practice." Furthermore, the Council "believes that charges should be made where possible under the existing laws of the state to the physician for all facilities and personnel involved in his private practice." It is regrettable that this action was taken in a unilateral form without adequate discussion and consultation with the universities and medical schools. The Council of the Association of American Medical Colleges made the following statement which I shall quote in detail. This was unanimously adopted at the fall meeting of the Association. It states:

> "There is abundant evidence of the willingness of the schools to work with the profession in the resolution of common problems. In fact, in most university centers, there is no conflict and the profession actively supports the university in its program for the school of medicine. There are a few loci of disagreement, but one may question that this calls for action at the national level, particularly when these loci of disagreement are in newly formed or expanding schools. This is proof that, given time, the schools and the profession have worked out their problems, without unilateral action by either party at the national level.
>
> "*Second,* it is a part of educational policy of the United States that overall direction of the educational institutions is in the hands of a Board of Trustees and a president or chancellor, acting on the advice of the deans and faculties. Such matters as organization and compensation of faculty and curriculum properly are within this jurisdictional pattern. It would be unfortunate for the future development of higher education in this country if we accepted a uniform and fixed pattern. Most of the significant advances which have been made in education have arisen through experiments by a few institutions. Universities cannot permit restrictions or impositions from outside to limit their conduct of the educational program.
>
> "*Third,* the Executive Council recognizes that the Council on Medical Services had the best of intentions in the preparation of a report on full-time which would be acceptable to all, and that the House of Delegates acted in what the majority of members believed is the best interests of medicine in this country, on both matters. Three members of the Executive Council had some opportunity to consult with the Council on Medical Services and its committee on hospitals and related facilities, but the final report on full-time was that of the Council itself, and not that of a joint group. Three clarifying changes were made at our suggestion just before the report was sent to the House of Delegates.
>
> "*Fourth,* at the February, 1956 meeting of the Executive Council of the Association, a statement on 'Meeting a Challenge to Medical Education' was approved. A copy of this is attached. It is the opinion of the Executive Council that this statement expresses well our position."

I may say that this statement expresses the opinion of medical educators in general and I shall read it as the present position of our American Medical Schools:

"*Meeting a Challenge to Medical Education*"

"The maintenance and improvement of the physical and mental health of the population are among the primary responsibilities of any nation. Health ranks in importance with other major features of the national economy, such as food supply, housing, employment, education, and industrial and agricultural production.

"The level of any health service depends upon the competence of those who participate in it.

"The future health of the people will depend in considerable measure upon the continuing supply of competent physicians. The education of physicians is a mutual concern of the universities, the medical schools, the teaching hospitals and the medical profession. The chief source of the supply of physicians will be the medical schools and teaching hospitals of the country.

"In order that the high standards of medical education both for medical students and resident training may be maintained, it is essential that the universities, the medical schools, the teaching hospitals, and the medical profession appreciate the problems created for medical education by the changing pattern of medical and hospital services, a growing emphasis on medical research and the complexity of the operation of a modern teaching medical center.

"The production of competent physicians by the teaching institutions will depend upon adequate facilities, financial support, the recruitment of a sufficient number of well-prepared students and particularly the maintenance of a staff of qualified scientists and clinicians dedicated to the education of physicians.

"Prepayment plans for hospitals and medical services, which have shown a phenomenal growth in the last ten years, are having a pronounced impact upon the operation and financing of those services. The cost of medical and hospital services continues to rise so that prepayment becomes more and more necessary. The growth of knowledge with consequent specialization within the profession has introduced many new problems, partly answered by the evolution of group practice, preventive medicine and emphasis again upon the whole individual and family as the unit of medical care. All of these and other developments have produced considerable disruption in the older methods and forms of practice.

"The hospital and medical service prepayment plans are sharply modifying an earlier concept of relying upon indigent patients in the hospital for the clinical instruction of medical students and residents. Medical education requires a satisfactory volume and balance of clinical material in order that the high level of bedside instruction be maintained. The steady diminution of ward patients will require a continuing readjustment in our approach to the use of private patients and those covered by prepayment insurance plans to insure the instruction of medical students and residents.

"Adaptations of medical and hospital services to the changing economic, social and professional conditions are to be expected. They have created apprehension and fear on the part of those who are obligated to meet new situations. These are evolutionary adjustments identified with progress, although new methods, just because they are different, are not necessarily better. These changes inevitably will have an impact upon the problems of professional education.

"In view of the heavy duties upon the staffs, particularly in the clinical departments, many medical schools have put some of the appointments in those departments on one or another type of full-time status in order to insure proper instruction of students, the conduct of research and the supervision of patient care. These developments have increased the effectiveness of instruction, the productivity in research and the quality of patient care in the hospitals.

"The teaching institutions which have the function of preparing the future generations of physicians should be encouraged to secure the services of full-time teachers and investigators under any reasonable plan satisfactory to the staff members and the school that will strengthen and improve the quality of medical education. They should have the support of the profession, the universities, and hospitals in their endeavors to maintain the quality of teaching which, in turn, will insure a high level of health service for the future. The teaching centers associated with medical schools should be concerned with providing patient care of the highest standard and in doing so in an ethical manner they should be free from hampering regulation and censure by the medical profession. The profession and the teaching institutions should work together to encourage legislation which will not restrict the teaching centers in performing their essential functions in a modern society."

In closing, I should like to say that in my judgment the full-time system of teaching in medical schools is here to stay. The problem of adequately financing it has become an ever-increasingly difficult one; however, when we realize that this method of conducting our medical educational programs is so vitally important to a high standard of work, all elements concerned must work together to expedite it and to support it. Many times misunderstandings are due to misinformation and adequate communication is most essential for our future programs.

REFERENCES

1. Flexner, Abraham. *Medical education in the United States and Canada.* A report to the Carnegie Foundation for the Advancement of Teaching. New York, 1910.
2. Deitrick, J. E. and Berson, R. C. *Medical schools in the United States in mid-century.* New York, McGraw Hill Book Co., 1953.
3. Fleming, D. The "full-time" controversy, *Johns Hopkins Magazine,* v. 6, no. 1, 1954: reprinted in *J. med. Education 30:* 398-406, 1955.
4. Hinsey, J. C. Full-time clinical faculty, *J. Amer. med. Assoc. 162:*16-19, 1956.

PROBLEMS IN MEDICAL EDUCATION*

PERRIN H. LONG

Professor and Chairman, Department of Medicine, College of Medicine, of the State University of New York, Downstate Medical Center, Brooklyn, New York

IN CONSIDERING the subject which has been assigned to me for discussion, I feel that its proper treatment necessitates wide definition to include remarks on certain problems in medical education, and also on its purpose. It would be too easy to say that medical schools and educational programs in hospitals exist primarily to produce intelligent doctors who have their patients' welfare as their major concern, and to provide medical scientists and teachers who will further research and medical education.

However, there are, I believe, a number of factors which have recently affected or will shortly affect, the aims and purpose of medical education and which, while touched upon at certain levels, have not, to my knowledge, become a matter of real concern either to our faculties or to the governing bodies of medical schools.

Not long ago, Professor Oscar Handlin of Harvard, in a stimulating article entitled *The Crisis in Teaching*,[1] pointed up the problems resulting from the over-population of existing primary school facilities in our country, and the immediate, as well as short term, effect which it will have on our secondary and collegiate educational programs in the next several years. Today there are over 30,000,000 children in primary schools as compared to less than 20,000,000 in 1945-46. We have more than 7,000,000 students in high schools. In eight years this figure will rise to more than 10,000,000. Slightly more than three million students are enrolled in colleges and universities in the current academic year. There is good reason to believe that within ten years our collegiate population will number more than five million students, and it might even approach eight million.

In 1954-55 about 15,000 students sought entrance to medical school.

* Presented at a meeting of the Section on Historical and Cultural Medicine at The New York Academy of Medicine, January 23, 1957, as part of a symposium on *The Future of Medical Education*. Manuscript received January, 1957.

In 1955-56 their number rose to over 16,000. If, in the next few years, the rise in applicants to medical school maintains its current ratio to students in college, one can expect that in ten years there may well be in excess of 30,000 applicants, and possibly even 40,000. Currently, there are about eight thousand places for entering students in the medical schools of this country. This represents an increase of slightly more than a thousand spaces in the past ten years. At present, about 1,400 American citizens are studying in medical schools outside of the United States and Canada. To maintain a normal increase in doctors, relative to the expected growth of our population to over two hundred million persons, one should have, in ten years, approximately 37,000 medical students in American schools, as opposed to the 27,000 who were in school in 1955-56. This means that facilities for the education of roughly 10,000 more medical students must be provided within the next ten years. It seems to me that a continuing aim of medical educators in this country should be to see that these facilities are provided. Otherwise, we will face making up the deficit in doctors from graduates of medical schools outside of this country. However, the provision of adequate physical facilities to take care of the probable increase in medical students will be of little value unless teachers are available, both in the Basic Sciences and Clinical Sciences, to provide the necessary instruction for the enlarged medical-student body. We must augment and strengthen our graduate educational programs at both the Basic and Clinical Science levels; otherwise we will certainly see a deterioration in standards of teaching and of medical education. This augmentation must be started today. Tomorrow will be too late, as it takes years to educate adequate teachers for medical subjects.

The next factor which I would like to discuss is the applicant to medical school, past, present, and future. In the most recent report of the Council on Medical Education and Hospitals of the American Medical Association[2], an analysis was made of the collegiate records of first-year medical students from 1950-51 through 1955-56. In 1950-51, 40 per cent of first-year medical students had left college with an A record. In 1955-56, but 16 per cent of first-year medical students had had an A record in college. In this same period the number of first-year medical students who achieved a B record in college rose from 40 to 71 per cent. Fortunately, the number of students who entered medical school with a collegiate record of C remained essentially the same. To

highlight this loss of A students, it can be said that between 1950-51 and 1955-56, 7500 fewer A students were admitted to first-year medical school classes than would have been the case if the trend noted in 1950-51 had been maintained. The loss of this group of students to medicine may well be reflected by a decline in the productivity of medical research and the adequacy of teaching over the next decade.

It is my belief that the figure quoted above represents an actual loss of first-rate college students who decided against a career in medicine. The reasons for this must be explored honestly. One only has to read the want ads, listen to radio, or view television, to witness the drive being made by American industry to influence the young people of today towards training in the fundamental and applied sciences. Industry's needs are extraordinary. A few years ago Boeing needed one engineer for every fifteen employees, today the ratio is down to one to ten, and Boeing is desperately searching for more engineers. The area of fission and fusion, the field of plastics, of electronics, of guided missles, of jet planes, of earth satellites, and other fields in basic and applied sciences are constantly being presented to the students of today, as the worlds of tomorrow. When these exciting vistas are coupled, as they currently should be, with the question of patriotism and of our national survival, their appeal is almost irresistible.

The monetary rewards are good, too. Practically any college graduate holding a degree in engineering or in the applied sciences is paid approximately five thousand dollars his first year out of college, and he has the prospect of doubling these earnings within five years. This is to be compared with the situation of many a young physician who makes essentially no money in the eight years required to complete his undergraduate and graduate medical education, and has a lean time for several years after his intramural education is completed.

Having just examined the situation relative to the collegiate scholastic records of the students currently entering or considering a career in medicine, I feel an inquiry should be made as to how many of these students are readily educable, and whether in certain areas of our country, due to restrictive devices which hamper sound admission policies, the bottoms of the lists of applicants are being scraped to produce the required quota for the entering class. As these two factors seem to go hand in hand, I shall treat them as a single subject. To begin with, if the word of certain of my colleagues who obviously must remain

anonymous, and who are in faculties of medicine whose admission policies are restricted by the wishes, publicly or privately expressed, of legislative or administrative bodies, can be taken at face value, then but one conclusion can be drawn. Students are being admitted to the study of medicine who, under truly academic policies of admission, would be rejected, because they would not measure up under a freely competitive admission system. The bottom of the barrel is being scraped.

One aspect of the question has puzzled me for some time, and it is one concerning which I can find little data. The collegiate academic records of students admitted to medical schools in 1955-56, show that over a thousand students were admitted who had C records in college. In that year roughly 8,000 applicants either were rejected or withdrew their applications. Why were those in this group rejected? For poor scholastic standing in college? Because of personality difficulties? Because of race, color, or creed? I wish I knew the answer as such relates to this group of applicants. If these applicants were unacceptable primarily because of poor scholastic achievement, then we should all be greatly concerned, because it would mean that currently the majority of applicants for medical school have mediocre collegiate records.

In 1955-56, over four per cent of the first-year class failed, or withdrew because of poor standing. While this may seem to be a small failure rate, all of us who are vitally concerned with medical education know of the soul-searching that goes on year after year in the minds of the faculty, relative to the problem of the lower fifth of the class, a group which remains remarkably consistent in its make-up, year after year in any medical school. I would like to raise the question whether well enough established guideposts exist to permit us to determine whether an applicant is going to be educable? What about the over-all reliability of medical admission aptitude and other tests, to which more or less attention is paid by admission committees? The well known president of a small liberal arts college has expressed the opinion recently that some colleges should limit their admissions to individuals who have a college board score of 550 or over, while other institutions should take care of those who have scores of 300 to 500.

Those applicants for college having a score of 300 or less, he considers to be real risks, as far as being able to gain stature intellectually from a college education. I will now ask, could and should we establish a score-level from currently used medical aptitude tests, which must

be reached prior to the consideration of an applicant for entrance into medical school?

Before leaving the problem of the potential medical student, I would like to speculate on the factors which motivate students to seek a career in medicine. It would be interesting to know the effect of a physician father or mother on the desire of their offspring to enter medicine. One might also inquire as to why more physicians' sons and daughters are not entering the profession. I also often wonder how many of our current applicants to medical school are motivated by an active social conscience which makes them want to do something for sick and disabled individuals, how many enter medicine because they are fascinated by the teaching and research approaches which may be found in this profession, and finally how many have chosen the profession of medicine, not because it seems the natural thing for them to do, or because of a desire to do something for suffering humanity, or as an approach to teaching and research, but rather as the quickest way to raise the individual from one economic and social stratum to another. It seems to me that we cannot set far-reaching goals in medical education without a knowledge of the motivation of those who want to enter our profession. Otherwise we may find that our basic educational premises are false, because if the ore is poor the yield will be low. I have also been wondering whether there is too much talk about geriatrics, because the problems of the aged do not seem to appeal to most youngsters, and also, as to whether the levity with which psychiatry has been treated in the public press has deterred thinking young people from entering our profession.

However, I do believe that this total situation can be remedied by an intensive campaign on the part of our profession and medical educators to influence bright young people to enter a career in medicine. To begin with, we must match our competitors' scholarship funds in our hunt for talent. Industry is expending hundreds of thousands a year to attract intelligent high-school students into collegiate programs in which industry has a special interest. The medical profession must do likewise through our own resources and those of the pharmaceutical industry. The media of communication which are open to industry are open to us, and it is my belief that we as a group should make more use of them. There are vehicles, especially in television, such as "Johns Hopkins File 7", "Medical Horizons", etc., which represent an appeal

to the interest in medicine of the American people, but I am afraid that we may have permitted our ethical standards to hamper the usefulness of these presentations in interesting young people in a medical career.

One of our goals as medical educators should be to obtain a fair share of the promising youngsters of this country for our profession. All should realize that we cannot have a first-rate system of medical education in this country without first-rate students. The excellence of the faculty is important, but without good students their efforts go for naught.

Furthermore, should not we, as a profession, explore the possibilities of shortening the time required for collegiate and undergraduate medical education? This is not a new idea, by any means. Like the weather, there is a lot of talk, but nothing's done about it. I for one believe that the time now generally spent in collegiate and undergraduate medical education, which is from seven to eight years, can be appreciably shortened without impairing the excellence of the product. For example, in the Medical Basic Sciences, using the data given in the most recent report of the Council on Medical Education and Hospitals[2], one finds that variations between minimal and maximal hours of instruction offered by various medical schools amount to 362 hours in anatomy, 340 in physiology, 194 in biochemistry, 278 in pharmacology, 183 in microbiology, and 354 in pathology. Using these differences between minimal and maximal teaching hours (which may well be an unfair approach), one finds that about 1700 teaching hours might be whittled out of the Basic Sciences, and used profitably to shorten the time required to produce a well rounded graduate in medicine.

As I do not wish to annoy my colleagues in the Basic Sciences, I will have a go at the Clinical Sciences. Here again, in my opinion, too much time is given over to subjects in the undergraduate medical program which should be taught in the intern and resident years. These include all the specialties, both medical and surgical. It is my belief that only the principles and not the details or techniques of the specialties should be exhibited to the undergraduate medical student. Furthermore, why shouldn't pediatrics and psychiatry be placed along with dermatology and neurology in medicine, from which they sprang? Pediatrics deals with disease in Junior and Junior Misses, while it is becoming apparent that one of the major problems in psychiatry, namely schizophrenia, results from a biochemical disturbance in the

body and not from emotivity. Also, in my opinion, it is time that psychiatrists left the couch side, and sought the bedside and became physicians once more. Is there not something odd about a photograph which recently appeared in *Life Magazine*[3] which shows in a team which takes care of emotionally disturbed *patients*, an individual listed as a physician, while another is labeled psychiatrist? Why is gynecology linked with obstetrics, except for the fact that these specialties deal with mothers and very new babies and females beyond puberty? Why can't we at the undergraduate level of teaching, destroy a number of the artificial bounds which have been created in medical education during the past hundred years, and which have resulted in the segregation of subjects rather than an integration of the same? Is our curricular structure the result of careful scientific inquiry into medical education, is it the result of empire building, or did it just grow like Topsy? I suspect that our present curricula probably are a combination of all three, although the development of fundamental and applied research in the Basic and Clinical sciences, and of clinical specialization, have played an important role in the development of our segregated, medical, curricular structure.

I feel reasonably certain that with the proper give and take among medical educators, the time required for adequate undergraduate education of the physician and teacher could be reduced certainly to six years, and conceivably to five years, without danger of producing graduates who are deficient. Of course, if this could be accomplished, the total curricular structure would have to be designed and controlled by university medical schools, otherwise an integrated curriculum would be difficult to maintain. It should be one of our aims, as medical educators, to reduce the time required for premedical and undergraduate education. If this can be done, there is a chance that more first-rate students will enter medicine. I believe, with a properly conceived undergraduate and graduate medical educational program of this type, based on general medical education, that we could more easily produce the *generalist* in medicine who is being sought so widely today. Because of the complexity of the subject, I will not have time tonight to discuss the proper integration of graduate medical education with undergraduate programs, a matter of great importance in a total medical education program. I would like to say, however, that frequently a real dichotomy exists in the education of a doctor between

his undergraduate and graduate educational programs, because while the educational aspects are paramount in his undergraduate years, those of the internship and residency are often secondary to the provision of medical service. This is particularly true of certain programs for rotating interns.

The question has arisen, and may become pressing if a marked increase in the number of applicants for entry into medical schools develops in the next decade, as to the ability of a medical school, possibly groups of medical schools, for example those which are directly tax-supported and those which are privately supported, to maintain excellence in medical education. I have been struck during my past five years in New York City, by the use of the terms *name* medical schools and *name* hospitals, by applicants for medical schools and by medical students who are seeking internships. The word *name*, in their minds, seems to be synonymous with *excellence*. Despite the fact that all medical schools in this country are classified as approved, the *excellence* of medical education and research, and of the raw student material with which medical schools have to work, varies considerably. The general characteristics of *name* medical schools are relatively small student bodies (for the facilities available) made up of first-rate students, low faculty-student ratios, broad and active research programs in both the Basic and Clinical sciences conducted by comparatively large full-time staffs, able and devoted volunteer and part-time faculty members, and voluntary hospitals in which patient care is maintained at a high level, thus affording the proper environment for clinical teaching. There are currently few, if any, indications that schools of this type are planning to increase their student bodies proportionately to the probable increase in applicants for admission to medical schools over the next decade. Their policy, which we will all agree with, is that they will not sacrifice the excellence of their educational, research or medical-care programs in order to produce more doctors. If this be true, shouldn't medical educators speculate on which schools will have to absorb the increasing number of applicants, as such is related to the future role of the tax-supported medical schools? It seems to me that one must admit that tax-supported medical schools can be and are subjected to legislative or administrative pressures in one way or another. One example of this is the fact that in eleven of our States, the tax-supported medical schools have restrictive policies relative to the admission of students. Another

which is developing, without seemingly counting eventual costs, is that of enlarging the student bodies in tax-supported medical schools to a degree disproportionate to the academic, research, and medical resources of these schools. This seems to be happening in a number of States. The question which I would like to raise is whether such increases in the student body can be made without lowering the existing quality of education in tax-supported medical schools, and must we be forced to visualize the development of what I will call medical schools with a conveyor line for the production of doctors? Are we witnessing the development of two standards of medical education, one of which will produce the custom-built physician, while the other will be devoted to the mass production of doctors? Should we, as educators, accept this as an inevitable tendency, or should it be one of our goals to combat it? I for one do not believe that the enlargement of the student body in tax-supported institutions will necessarily produce a deterioration in the standards of medical education, *if administrative and legislative authorities do not force restrictive admission policies on those schools, and do provide favorable facilities, together with budgets which will ensure the continuing support of adequate full-time, part-time, and voluntary faculty bodies, and of a well rounded research program.* This is a matter of generous appropriations. My worry is, and I can tell you it is a real one, that as the costs of medical educational institutions are high, and will increase (along with the costs of everything else), administrative and legislative bodies, having to economize somewhere, will feel that it can be done in the field of medical education. This is the danger, because it will promptly bring about a reduction in the standards of teaching and research, which means a lowering of the standards in medical education and research in institutions affected by such programs. Medical schools are in a highly competitive era for first-rate research and teaching personnel, and when budgets are inadequate, top-flight personnel goes elsewhere.

Only the immediate and continued aggressive action of enlightened administrative and legislative bodies can prevent the evolution over the next decade of many tax-supported medical schools into institutions for the conveyor-line production of inferiorly trained doctors. Those who are responsible for medical education would do well to remember that excellence in teaching, research, and medical care should be their prime concern in any consideration of their institutions for medical

education, and that they should allow themselves no choice but to make every effort to permit their teaching centers to carry out their programs with distinction. They must not permit the pressures for larger enrollments to tempt them to lower standards. As Jacques Barzun has recently warned, "To expand for the sake of a mere numerical show should be akin to demagogy, especially if done in the name of civic duty. And from the truly social point of view it would amount to debasing the coinage—a poor gift to the unsuspecting student seeking our degrees, and to the community that would accept them at face value." None will be forgiven if they do it. Tax-supported medical schools must not be forced to compromise their educational standards simply to accommodate more students, because a lowering of these standards will mean that the citizens who are footing the bill are being defrauded as they will eventually receive poorer medical care.

If this happens, we will have to downgrade the old and respected definition of physician and mediocrity will become enshrined in our profession.

REFERENCES

1. Handlin, O. Crisis in teaching, *Atlantic Monthly 198*, no. 3:33-37, 1956.
2. Turner, E. L. and others. Medical education in the United States and Canada. Fifty-sixth Annual Report by the Council on Medical Education and Hospitals of the American Medical Association. *J. Amer. med. Assoc. 161*:1637-69, 1956.
3. *Life 42*, no. 1:60, 1957.

ERRATUM

In the previous issue of the Bulletin, November 1957, the name of Robert McC. Day was inadvertently omitted as a co-author of the article *Ten Year Results of 1-131 Therapy of Hyperthyroidism*, pp. 783-806, by Sidney C. Werner, Bento Coelho, Robert McC. Day and Edith H. Quimby. The Editor deeply regrets this omission.

THERAPY OF DISEASES OF THE GALLBLADDER AND BILE DUCTS

*Transcription of a Panel Meeting on Therapeutics**

J. Russell Twiss . . . Moderator

Associate Professor of Clinical Medicine, New York University Post-Graduate Medical School; Attending Physician, University Hospital

Panel Members

Albert F. R. Andresen

Clinical Professor Emeritus of Medicine, State University of New York, College of Medicine at New York City; Attending Physician, Long Island College Hospital

Franklin M. Hanger

Professor of Medicine, College of Physicians and Surgeons, Columbia University; Attending Physician, The Presbyterian Hospital

Howard A. Patterson

Clinical Professor of Surgery, College of Physicians and Surgeons, Columbia University; Chief of Surgical Service, Roosevelt Hospital

William H. Shehadi

Professor and Director of Radiology, New York Polyclinic Medical School and Hospital

* Presented at the Monthly Panel Meeting (Fourth Series), at The New York Academy of Medicine.

MODERATOR J. RUSSELL TWISS: Our subject this afternoon, "Therapy of Diseases of the Gallbladder and Bile Ducts", is important because gallbladder disorders are the most common cause of digestive disturbances, and one of the most common causes for abdominal operations, particularly in the aged. We are most fortunate in having for the discussion of this subject a distinguished group of specialists, each with broad experience, each well known as an investigator, a writer and a teacher. On the far right is Dr. Franklin M. Hanger, next is Dr. William H. Shehadi; on the left is Dr. Albert F. R. Andresen, and on the far left Dr. Howard A. Patterson. The program will consist, first, of a brief presentation by each panelist on a selected subject in this field; followed by a thirty minute question and answer period for written questions from the floor. If you have questions to present, please address them to a specific member of the panel and please make the questions brief and concise.

As an introduction, the panelists have asked me to precede their discussions by an outline of differential diagnosis. Successful management in this field is dependent upon the correct initial diagnosis and a prompt decision as to whether the treatment in any given case should be medical or surgical. Medical management is indicated for functional disorders and so-called catarrhal conditions of the biliary tract. For these, surgery is contraindicated and may be detrimental. Surgery, on the other hand, is required for all patients with organic disease, especially those with obstructive or inflammatory lesions, to prevent complications and irreversible pathological change. The basis of this diagnosis and decision in each case should be a comprehensive diagnostic investigation, the results of which may be summarized as follows:

In regard to the history of the functional disorders the common symptoms are dyspepsia and indefinite gas-discomfort after meals, pain, intolerance to fat, and constipation. With organic disease, on the other hand, the predominating symptoms are usually colic, with which there may be nausea, vomiting, chills, fever, jaundice, or loss of weight and strength. Usually none of these symptoms are found in the functional disorders. On physical examination we have a conspicuous finding in the functional cases of an extreme degree of internal tension, characterized in many patients by an irritable colon and hyperactive reflexes, the so-called "ulcer type" of personality. In the organic group physical examination may reveal tenderness of the gallbladder or liver. The gall-

bladder, is sometimes palpable, if there is a calculous obstruction of the cystic duct or a non-calculous obstruction of the common duct. There may be a mass in the right upper quadrant with inflammation or neoplasm of the gallbladder. There may be jaundice or emaciation. The x-ray examination in functional cases usually shows a normal visualization of the gallbladder, although there may be a delay in emptying. In organic disease, on the other hand, there is usually no visualization, or very faint visualization of the gallbladder. Stones may or may not be visualized.

Among the optional tests which are frequently of value when the diagnosis is in doubt, is a duodenal drainage, which, if properly performed, gives very definite valuable diagnostic evidence as follows: in the functional disorders we are very apt to find gastric hyperacidity. We usually obtain concentrated gallbladder bile, with microscopic examination of the bile sediment. Cultures of the bile are usually negative. In organic disease, we frequently have achlorhydria and often no concentrated gallbladder bile. Microscopic examination may show pathologic elements in the nature of crystals, pus, blood or cancer cells by the Papanicolaou technique. Cultures may show evidence of pathogenic organisms. Chemical blood examinations, which should be done in all seriously ill patients, give positive findings, whereas in the functional disorders they are usually normal. In organic biliary disease there may be increased bilirubin, serum alkaline phosphatase, cholesterol and evidence of impaired function of the liver or pancreas.

The first of the selected subjects to be discussed by the panelists will be the physiologic basis for therapy by Dr. Albert F. R. Andresen.

DR. ALBERT F. R. ANDRESEN: Empiricism is supposed to have been abandoned in medical practice. Yet, in biliary tract diseases the treatment of symptoms is today still the most frequently practiced form of therapy. Heartburn and belching are treated with antacids, spasmodic pain with antispasmodics and anticholinergic drugs, severe pains with analgesics and hypnotics, nervous symptoms with barbiturates, fever with antibiotics, indigestion from fat by a fat-free diet, hypercholesteremia by a cholesterol-free diet.

The rational and most effective treatment of biliary tract diseases must be based on a knowledge of biliary tract function. We know that the liver pours out continuously from 800 to 1500 cc. of bile per day, which passes down through the hepatic and common ducts to the

duodenum. Although partly an excretion, the bile contains bile acids and salts essential to fat digestion. Nature has provided that when there is no fat in the duodenum, the sphincter of Oddi, located at the entrance of the common duct into the duodenum, closes, and thus prevents the bile from being wasted. The bile then backs up and by a sort of safety-valve action goes through the cystic duct into the gallbladder where it is stored and concentrated ready for efficient fat digestion when called upon. When fat is ingested, two mechanisms are set in motion:

1. The hormone, cholecystokinin is formed and when absorbed and carried to the gallbladder causes it to contract;

2. When fat comes in contact with the duodenal mucosa it causes the sphincter of Oddi to relax, so that the concentrated bile can be delivered to the duodenum when most needed.

That fat is the most efficient substance to produce this effect has been amply demonstrated by x-ray studies, fat being used to determine whether the gallbladder can contract. Failure of sufficiently frequent emptying of the gallbladder, whether from disease or from insufficient or too infrequent ingestion of fat, causes increasing concentration of bile in the gallbladder, producing inspissated bile, which may interfere with emptying, or actually may allow bile to precipitate out in the form of stones.

In biliary tract disease the first and most desirable form of treatment is to promote adequate drainage of bile into the duodenum. It has been shown that ingestion of fat, emulsified or whole, in the form of butter fat, egg fat or vegetable oils, is most efficient in promoting this drainage. Its effect in various types of biliary tract disease has been demonstrated by x-ray studies.

In Oddi sphincter spasm, whether from local disease, nervous causes or drugs, administration of fats will produce relaxation.

In common duct obstruction, if due to inspissated bile, this may be dislodged; if due to stone, it may have no effect. More frequently, however, it may produce sufficient *vis a tergo* to move the stone downward. I have never observed a perforation to occur as a result.

In cystic duct stone, a steady flow of bile through hepatic and common duct may, by a sort of suction, encourage the stone to pass.

Inspissated bile, even so-called "muck" or sand, can usually be gradually eliminated by the diet.

Also, a so-called "non-functioning gallbladder" can frequently be restored to normal function in less than six or eight weeks, even though showing stones or appearing as a normal gallbladder.

In the presence of stones in the gallbladder, a fat-free diet or infrequent feedings permit the distention of the gallbladder with bile. Then, when the gallbladder contracts in response to a large fatty meal, a stone may be forced into the distended neck of the gallbladder or into the cystic duct, causing colic. Frequent feedings with adequate fat will almost invariably prevent this unfortunate sequence of events.

In acute cholecystitis there certainly can be no contraindication to adequate biliary drainage, which will prevent too much bile from going up the cystic duct to the gallbladder. As a diseased gallbladder could not be expected to contract from hormone stimulation, it cannot be harmed by this treatment.

Postoperatively, the prompt institution and long continuance of frequent, fat-containing feedings, will almost always prevent the so-called "post-cholecystectomy syndrome".

MODERATOR TWISS: Thank you, Dr. Andresen. Next, Dr. Hanger will discuss diagnostic tests with their indications for therapy.

DR. FRANKLIN M. HANGER: The history, physical examination and x-ray studies are the most valuable methods of making the diagnosis in gallbladder disease. We must realize, however, that many other clinical conditions can simulate cholecystitis, cholangitis, biliary colic, etc., and give rise to upper abdominal pain and tenderness and jaundice.

Let us think first of the liver—a tender liver can be very prominent in hepatitis. It is also common in chronic passive congestion, and in the post-hepatitis syndrome. It is observed in people who have a splanchnic congestion during certain phases of digestion, also with liver abscess, tumors and infections of the bile ducts. I have seen patients with viral hepatitis operated upon for a suspected gallbladder disorder because of the extreme pain and tenderness in this region. There is no single test that differentiates diseases of the liver from those of the biliary tree. Viral hepatitis is characterized by low white count and by an elevation of prompt reacting bilirubin in the serum. The cephalin flocculation test is positive in about 90 per cent of cases and the alkaline phosphatase is usually elevated at onset.

A distinguishing feature between the jaundice picture of hepatitis and that of an extra-hepatic obstructive process, lies in the fact that the

akaline phosphatase level is highest at the beginning of hepatitis and tends to subside rather promptly while the bilirubin rises quickly and independently to its peak. In contrast, obstructive processes usually are characterized by a gradual elevation of serum alkaline phosphatase and serum bilirubin and the two tend to rise concomitantly. It is desirable to get an initial base line of these studies early in the disease for it is the *course* of these two tests which can be most helpful in making a correct diagnosis in puzzling cases.

We must also consider the pancreas. Pancreatitis is a frequent feature of biliary disease. We know that pancreatitis and biliary disease may occur concomitantly. The serum amylase may be extremely important. Here again, the timing of the test is of great significance, because the serum amylase level is most revealing at the time there is pain and during the acute episode but may show normal values after a few days.

Diseases of the right kidney must also be considered. I have seen cholecystectomies, or exploration of the biliary tree for pain in the upper right quadrant, which eventually were proved to be due to a lesion of the kidney or to a retroperitoneal tumor. When we encounter patients with upper abdominal pain but with normal gallbladder studies, pyelograms and even air insufflation of the retroperitoneum may eventually be indicated to rule out renal and perirenal pathology.

The colon is notably capricious and may cause quite severe pain in the upper right quadrant which is disturbing both to the patient and to the clinician.

The heart also can be a very difficult organ to evaluate. Patients with acute coronary disease may have pain radiating to the epigastrium. Patients with coronary disease or acute coronary occlusion may also have a sudden failure of the right heart with an acute congestion of the liver, which is so painful that it dominates the picture. It is this group of patients with coronary attacks who develop jaundice in the days following the acute episode. Sometimes, if we don't notice the temporary swelling of the liver initially, we do not make the correct diagnosis. In these cases venous pressure studies or electrocardiograms may give significant findings. A careful auscultation of the heart may reveal a friction rub, which is very important. Irritation of the right pleura also can cause referred pain to the upper right quadrant.

Certain blood diseases such as sickle cell crisis can give rise to acute

abdominal symptoms that simulate a gallbladder attack very closely. Hemolytic diseases also predispose to the formation of bilirubinate stones in the biliary tree, so that we must differentiate hemolytic crises from true biliary colic.

Another aspect of biliary disease is fever. We must consider the gallbladder in our search for the cause of unexplained pyrexia. Cholecystography is an important routine in all such cases.

We also encounter patients with masses in the upper right quadrant and here again differentiation between biliary and hepatic disease may be difficult since tumors and abscesses or cysts of the liver and sometimes a normal Riedel's lobe can simulate enlargement of the gallbladder. The digestive disturbances of gallbladder disease may be confused with peptic ulcer, neoplasms and functional derangement of the alimentary tract. Even when biliary disease is demonstrable, often further studies such as stool guiacs and G.I. x-rays reveal the coexistence of other disorders.

How to evaluate all these mimicry considerations without bankrupting the patient? I think "clinical feel" and experience usually temper the thoroughness of our work-up. I do plead, however, for a certain minimal routine investigation. Every patient should have a red count, a study of the blood smear and a white count with a differential. These studies can tell us a great deal, not necessarily about the gallbladder but about other systemic diseases which may be present. Urinalysis also is indicated not only to determine the status of the kidney but to learn whether there is bile in the urine—after an early manifestation of gallbladder disease or hepatitis. A stool examination is mandatory. It should be searched for blood. It should be examined for urobilin and even the finding of parasites can be significant.

Another feature of the gallbladder problem is the general condition of the patient. Elderly patients particularly, have weaknesses in various systems due to the ravages of time. In general we must evaluate the cardiac status and must be sure the patient has no chronic pulmonary infection, or at least has enough pulmonary reserve to carry him through a serious operation. We must study the serum proteins a bit because all of you know how loath surgeons are to operate on patients with low serum albumin. Obesity and related conditions are other considerations which determine general clinical management.

MODERATER TWISS: Thank you, Dr. Hanger. Dr. Shehadi will now

discuss recent developments in roentgen ray diagnostic procedures.

DR. WILLIAM H. SHEHADI: In order best to appreciate what is available to us at present in the way of recent roentgen diagnostic developments, I would like briefly to review the various stages through which roentgen examination of the biliary tract has progressed. You will be interested to know that at the meeting of the Medical Society of the County of New York on October 16, 1899, the first recorded case of gallstone, diagnosed by x-ray, was presented by Dr. Beck. Upon examination of a plain film of the right upper quadrant two calculi were found in the gallbladder region and were removed at operation. This was the first case in which the diagnosis of gallstone was made by x-ray and proved by subsequent operation.

For 25 years thereafter, no great progress was noted until the very great contribution of Doctors Graham and Cole of St. Louis. They produced tetraiodophenolphthalein, an iodinated compound, which had a selective excretion through the liver, and, dissolved in bile, entered the gallbladder. That was indeed a great contribution which enabled us to study the gallbladder function,—its filling and its emptying and the ability of its mucosa to absorb and concentrate as well as the ability of the muscularis to contract. That contrast medium was not perfect. There were shortcomings. There were many side reactions.

In 1940 another contrast medium, Priodax, became available to us. Both of these media have two iodine atoms in the molecule. Priodax was a great improvement over tetraiodophenolphthalein which Graham and Cole produced. However, that too was not perfect.

A new era began in 1949 when the chemists gave us a compound that had three iodine atom molecules. This three-iodinated compound gave us excellent visualization of the biliary tract, better visualization of the gallbladder and, for the first time, consistent visualization of the biliary ducts. That was a very considerable improvement. However, one further step was made about three years ago when a six iodine atom molecule was produced for intravenous injection, Cholografin, as it is known in this country and Biligrafin as it is known in Europe. Telepaque, the first three iodine atom molecule, gave improved gallbladder visualization and also gave us bile duct visualization. Cholografin did not depend upon concentration by the gallbladder but on the high iodine content of the molecule; this made it possible for us to visualize the biliary tract just as the bile and the Cholografin came through the biliary tract. The pro-

gress made so far enables us to evaluate adequately, either by Telepaque orally, or by Cholografin intravenously, the entire biliary tract, the gallbladder and the ducts, in a manner very similar to that in which we visualize and evaluate the entire urinary tract. That of course has been our goal and it has now been achieved. A little later I will discuss and present to you slides showing some of the advancements that have been made.

MODERATOR TWISS: Thank you, Dr. Shehadi!

Dr. Howard Patterson will now discuss the relationship of gallstones to heart disease.

DR. HOWARD A. PATTERSON: I would like to speak very briefly about the association of gallstones and heart disease. This is an old question and there is little new about it as a problem.

Some of you perhaps know that the great John Hunter, probably the greatest name in the history of British surgery, died at a hospital board meeting in an anginal attack. His personal physician and close friend, Dr. Edward Jenner, predicted during life that John Hunter had both gallstones and coronary disease and that there was an association between the two. Autopsy proved that he was correct,—at least John Hunter had both conditions.

I think the question may readily be divided into three problems: first the problem of mimicry. We know that the type of pain is similar at times and that cardiac pain can be largely upper abdominal and that pain from gallbladder disease with calculi can be almost entirely thoracic, so it is easy to confuse them.

The second problem is that of co-existence. When you know that the patient has both heart and gallbladder disease, you try to determine how much of the presenting picture is associated with the gallstones and how much has to do with the coronary disease.

The third thing to determine is whether or not one can benefit the coronary disease by removing the gallstones. In other words, do the gallstones make worse an existing coronary disease? Of course it is easy for the skeptic to say,—"gallstones are far more common in women and coronary disease is more common in men. This is all quite foolish, and there is no relationship at all". Dr. Paul White, has written as follows: "A troublesome gallbladder may seriously disturb cardiac function in the presence of otherwise silent coronary disease", which is a rather definite statement. Experimental work goes back to 1909 and has been

voluminous. Dr. Ravdin and associates, at the University Hospital in Philadelphia, have developed a new method, which appears to be valid, of demonstrating that stimuli from the biliary tract can affect coronary flow very markedly.

This leads us to consider the advisability of performing cholecystectomy as a means of benefiting many patients suffering from both heart disease and gallstones. Fortunately this procedure has been followed rather frequently and, with suitable anesthesia, such patients stand surgery surprisingly well. A word of caution must be added because many patients with gallstones of long standing have no evidence whatever of heart disease. However, all patients with heart disease are not benefited by removal of their gallstones and may succumb to a fatal coronary occlusion during operation or soon thereafter. But with thorough evaluation and study of all the factors involved, this field of surgery is relatively safe.

I would like to close by mentioning, briefly, one typical case report. An old gentleman, the father of one of our graduate nurses, awoke one night suffering severe substernal pain with sweating and shock. He lived in a small community and had to be removed by ambulance some distance to the nearest hospital. At the hospital he was placed in an oxygen tent and remained in it for about two weeks. Eventually he was sent home. However, as a result of the advice given him at the hospital he was afraid to walk upstairs. Accordingly, he took all his savings and remodeled his house, building a bedroom and bathroom on the ground floor. No sooner had he completed this reconstruction when he suffered a second attack. His daughter made a diagnosis of cholelithiasis and brought him to Polyclinic Hospital, where a cholecystectomy was performed. Now, at 77, he has had no further difficulties and our latest report of him is that he was climbing a ladder with agility while painting his house. This case is a rather dramatic instance of "mimicry", a matter of mistaken identity.

MODERATOR TWISS: Thank you, Dr. Patterson!

Among the questions we have here, is one for Dr. Hanger: In early jaundice, how can chemical blood tests differentiate between intra- and extrahepatic disease?

DR. HANGER: Sometimes they can't. As you know the virus of hepatitis attacks the liver in several areas. It can produce necrosis of the liver parenchyma. When that takes place the cephalin flocculation becomes

positive rather quickly. The thymol turbidity becomes positive. If we have a patient with a positive cephalin flocculation and jaundice, I think the surgeons have learned that it is not wise to rush into operation. I believe the old aphorism, that jaundice is never a surgical emergency, probably should be remembered by all of us. The virus of hepatitis may spare the parenchymal cells but attack the cholangioles (the small collecting branches of the biliary tree), causing them to swell and produce intrahepatic obstruction, which can simulate extrahepatic obstruction in every way. In these cases the cephalin flocculation may be negative and the elevated alkaline phosphatase and the elevation of serum cholesterol point to an obstructive process. You might say, could we do a liver biopsy and distinguish these? I think any needle biopsy on patients with the chemistry of obstructive jaundice is rather hazardous. We are much more apt to produce bile peritonitis in this group. We can also produce bile embolization. But more important, the lesion that we find in the liver, namely, swelling and infiltration of portal triads is not diagnostic since it can be found in both extrahepatic obstruction and viral cholangiolitis. Therefore when we have this type of problem it is better to observe the patient by repeated tests, as I have indicated, and if the jaundice continues to rise, the alkaline phosphatase continues to rise, the urine continues to show bile, the stools show the absence of urobilin, the indications are more and more for surgical exploration. Even when we are reasonably sure that we are dealing with a cholangiolitic hepatitis, if the tests all indicate a progressively worsening process over three, four or five weeks, particularly in the elderly age group, I feel that those patients require examination by a surgeon rather than to rely upon further observation or the results of needle biopsy.

MODERATOR TWISS: *I have another question for Dr. Hanger: Are chemical blood tests of value in differential diagnosis of extrahepatic obstructive lesions?*

DR. HANGER: Sometimes these tests are more misleading than helpful. In my experience, in hepatitis there is never complete absence of bile in the stool for longer than two or three weeks. The routine examination of stools, not with the eye, but by chemical analysis for the presence of urobilin is most helpful because carcinomas of the pancreas and other serious organic lesions tend to cause complete and persisting absence of bile and urobilinogen in the stool. Acholic stools are a very serious finding, if carefully noted over a period of several weeks. Stones in the

common duct and cholangitis do cause intermittent biliary obstruction and to that extent make it difficult to rule out a partial obstruction from a cholangiolitic hepatitis. Other features of the case of course help a great deal. In some of these patients, while we are vacillating, we find that the gallbladder has become quite large and dilated. That finding is worth any group of liver function tests I know and is a mandate for surgery. I have observed that in these difficult cases where we know there is an obstructive factor to the jaundice, a careful repetition of tests at weekly intervals with an evaluation of the trend is probably our most valuable method of distinguishing a hepatogenous condition from an extrahepatic obstruction requiring surgery. I may say in this connection that I don't feel that surgery in patients with cholangiolitic hepatitis is nearly as dangerous to the patient as in those with a positive cephalin flocculation which is indicative of diffuse parenchymal damage. We do not hesitate to recommend operation to these patients, even when we know that intrahepatic inflammatory lesion of the biliary tree has not been completely excluded. The greater hazard is to prolong observation in patients with biliary obstruction.

MODERATOR TWISS: *I have a question for Dr. Shehadi: What is the best technique for cholecystography?*

DR. SHEHADI: At this time we feel that the best technique is by utilization of Telepaque as a contrast medium. The day before the examination a scout film is made and an evening meal that contains some fat should be given. Our observations from an x-ray point of view are much in accord with what Dr. Andresen mentioned a little earlier. In order to insure filling of the gallbladder we would like to evacuate whatever inspissated bile or accumulated bile is in the gallbladder. So we encourage a supper that contains a glass of milk, maybe an egg, one or two pieces of butter or some cream. That meal will invariably, if the gallbladder is filled, empty it much more readily. Only last week we had a patient whose gallbladder failed to visualize. He had been on a fat free diet for a long time and the first time he took the Telepaque the gallbladder did not fill. I prescribed the special supper and contrary to his physician's advice I insisted on the details. When he took a supper containing some fat the gallbladder visualized the following day. After such a supper, at about ten in the evening, six tablets of Telepaque are taken by mouth and in 10 to 12 hours, or about nine o'clock in the morning, a series of films are made. We insist that films be made not

only in the prone position but in other positions as well, in oblique and in the upright position; the latter especially brings about a stratification of calculi which otherwise could not be visualized. Once we establish filling of the gallbladder, we give a fat meal. The one I prefer particularly is a glass of milk with yolks of two eggs and a third amount of cream, an eggnog of about 8 ounces in all. Within 10 to 15 minutes films will demonstrate emptying of the gallbladder and filling of the ducts, and in about 40 minutes after administration of the fat meal the gallbladder, if normal or not obstructed, should empty completely. That is the basic routine used. Modification in the form of spot films, compression films, and lateral decubitus films can be made in selected cases. We insist on the use of fat. We insist on the use of multiple positions and to bring about the best results, we insist upon inspection of each film as it is made.

MODERATOR TWISS: *The next question is also for Dr. Shehadi: Is the normally visualized gallbladder always normal?*

DR. SHEHADI: Maybe we could say is the apparently normal visualized gallbladder always normal? Yes and no. If the gallbladder is filled we have an indication of the patency of the path into the gallbladder. If the gallbladder concentrates its contents we know that the mucosa is functioning adequately. If the gallbladder empties its contents, we know that the muscularis functions adequately. However, minute calculi may be present and may be concealed, but in the upright position their presence can be demonstrated. Sometimes tumors and polyps may also be concealed but with spot films and with special projections we can reveal those so that if we look at an apparently normal gallbladder and evaluate it further and insist on complete or almost complete emptying, we will be able to tell whether it is truly a normal gallbladder or an apparently normal gallbladder.

MODERATOR TWISS: *Another question for Dr. Shehadi: How do you interpret non-visualization of the gallbladder and what tests are confirmatory?*

DR. SHEHADI: Non-visualization of the gallbladder may be due to two causes. One is a group of causes which are extraneous to the gallbladder. Should disturbances of the gastrointestinal tract be present such as gastric retention, diarrhea due to one of many causes or failure of absorption through the small intestines, the gallbladder will not visualize. The gallbladder will also not visualize because of intrinsic changes in the

biliary tract. Of course, if the main hepatic duct is obstructed, then jaundice will be apparent. But if the cystic duct is obstructed or if there is a calculus not only in the cystic duct but in the neck of the gallbladder, the gallbladder will not visualize because bile and bile-containing contrast media will not flow into the gallbladder. Also a very chronically inflamed gallbladder, markedly reduced in size, with the lumen markedly reduced in caliber, will not visualize. We must make sure we evaluate these cases adequately and find out if there are causes outside the biliary tract which account for the condition.

With the use of intravenous cholangiography, as indicated before, we can now bypass, so to speak, the alimentary tract. If, after giving Telepaque by mouth, the gallbladder does not visualize we give Cholografin intravenously. If the biliary tract does not then visualize, we are quite certain that the gallbladder is diseased.

MODERATOR TWISS: *Here is a question for Dr. Patterson: How does improper selection of patients for surgery contribute to the poor surgical results?*

DR. PATTERSON: I think as the surgeon looks back on his failures and errors in gallbladder surgery, he is apt to find most of the unsatisfactory results in those patients who did not have gallstones. The surgery of the non-calculous gallbladder is a rather discouraging field of endeavor. We know that some of the patients who have a moderate or severe degree of cholesterosis of the gallbladder do well. However, if in those who have only a few adhesions around the ampulla of the gallbladder, one hopes to relieve the symptoms by surgery, it will be found that most of the failures are in that group.

In short, the surgery of the calculous gallbladder is a rather happy field of endeavor and the surgery of the non-calculous gallbladder is not. Why is that? I believe it is because it is often associated with errors in diagnosis and a common cause of error is the presence of hiatus hernia. The patient presents symptoms which, perhaps with a fairly adequate work-up, are attributed to gallbladder disease. The gallbladder is removed, yet the symptoms persist. The patients get up in the middle of the night, sit and sleep in a chair instead of sleeping in bed and find that they are just as miserable as they were before,—all due to hiatal hernia. There are also other instances of mistaken identity and errors in diagnosis from other causes. One quite common cause of failure is an inadequate work-up, after finding cholelithiasis. The patient says "I have been

feeling puffy and a little bit distended off and on for the last few months". Someone says, "She looks like the gallbladder type" and some films are taken which show a gallbladder full of stones. Whereupon the gallbladder is removed and in spite of the fact it is an elective case and is done in a quiet phase, the surgeon fails to examine the entire abdomen by palpation and inspection and he misses an annular carcinoma of the sigmoid. Then perhaps on the sixth or eighth postoperative day he has an intestinal obstruction to deal with. Except in some of the emergency or semi-emergency cases with acute cholecystitis, a thorough study of the patient is of course required. If that thorough study is not done before operation, the surgeon owes it to the patient to examine the abdomen carefully from the diaphragm right down to the bottom of the pelvis. Then, at least, he will learn what he missed.

MODERATOR TWISS: *Another question for Dr. Patterson: How should acute cholecystitis be diagnosed and treated?*

DR. PATTERSON: This is a question about which good friends used to have violent arguments and disagreement! I think that in recent years the difference of opinion is largely due to a confusion of terms. Somebody goes to a meeting and hears a well known experienced surgeon say that all of these cases should be operated on within 24 hours, that if they really have acute cholecystitis the operation is easier if done promptly, that the edema assists the dissection and that it is very important to do it quickly. So the surgeon goes home from the meeting. He sees a case a few weeks later and he operates on the patient immediately. He has a terrible time and so does the patient, because he thought the surgeon speaker had been talking about the number of hours in the hospital whereas he had been talking about the number of hours after the onset of the attack. If the patient has an attack of acute cholecystitis and is admitted to the hospital promptly, it is true that the surgery is usually easy and cholecystectomy is certainly the treatment of choice. When the patient has been at home for a week or ten days with an attack of acute cholecystitis that comes and goes, one day he is a little worse, the next a little better, he often becomes discouraged and eventually goes to the hospital. Technically, this is about the most difficult time to operate on him.

One thing that has always puzzled me is that whereas calculous gallbladder disease is commoner in women the severe fulminating types of acute cholecystitis are commoner in men. Almost any series will show

60-70 per cent of men in the severe fulminating cholecystitis group.

Another puzzling thing is that a certain percentage, 2, 3, 4 or even 5 per cent, in a series will have no gallstones but have a gallbladder full of pus. They have an acute empyema of the gallbladder without stones and I have never understood why that is. A few of these infections are due to Welch bacilli, but various organisms may be responsible for this rare condition. That is about the only type of non-calculous gallbladder upon which one should operate.

MODERATOR TWISS: Thank you, Dr. Patterson.

We have now some questions for Dr. Andresen: What are the types of diets used in gallbladder disorders and what are the indications and contraindications?

DR. ANDRESEN: The most common diet, of course, is the *fat-free diet*, which I have been fighting for the last 30 years or more. That is the one that seems to have become standard, for some reason. The patients find it unpalatable. As a rule it causes anorexia. The patients I see who have been on this diet are usually emaciated and weak, often dehydrated and show signs of various nutritional deficiencies. Such a diet is unbalanced. Fat is necessary for nutrition and for the assimilation of the fat soluble vitamins. It interferes with biliary drainage and so is apt to cause biliary stasis. There are many reasons why I don't like it but these are just a few.

In cases where acute pancreatic necrosis is suspected, feeding by mouth is avoided, continuous gastric suction is performed and parenteral feedings are given. Dr. Patterson will agree that it is of help in acute pancreatic necrosis. The trouble is that it is so difficult to differentiate between acute pancreatic necrosis and other types of acute abdomen. I believe in most cases, as Dr. Patterson has pointed out, that if you see an acute abdomen, it is safest to operate as soon as possible.

A *high fat diet* has been used. I used to recommend that myself. It is often useful at the onset of treatment and I find it of use during an attack of colic. Contrary to what some people believe, that diet would contain extra cream, butter fats and oils, like the meal that Dr. Shehadi spoke about in connection with preparation for gallbladder x-ray examination.

I believe that the gallbladder patient is entitled to a well balanced diet with proper proportions of carbohydrate, protein and fat, with the quantity of fat sufficient to cause adequate drainage of the biliary tract. To accomplish frequent, practically continuous drainage, I give

between-meal feedings. I used to give a milk and cream mixture between meals and at bedtime. I found that the cream is not necessary. Experimenting with x-ray, we found that instead of cream a heaping teaspoonful of plain gelatin either mixed with the milk or taken separately mixed, not dissolved in water, and the milk following it, will have about the same effect as a fat meal in emptying the gallbladder. A diet of three balanced meals with these extra feedings will promote adequate biliary drainage. It also provides adequate nutrition and is palatable if it is properly planned.

MODERATOR TWISS: *Another question for Dr. Andresen: What are the common causes of post-cholecystectomy syndrome and how are these treated?*

DR. ANDRESEN: The first question comes up: What is the post-cholecystectomy syndrome? I have never been able to find out just from reading what is meant except it is the condition of a patient who has been operated on and either isn't any better, has a continuation of the same symptoms or has developed some new symptoms. I think that is about the nearest one can come to defining it.

Dr. Patterson has already pointed out some of the reasons for those symptoms namely, unjustifiable operations, operations after inadequate study, operations where no stones are demonstrated before operation or found at operation, the presence of other conditions or complications that have not been evaluated before or during the operation including hepatic, cardiovascular, renal, pelvic or other diseases, and operations on patients with such infirmity or old age that surgery should have been avoided if possible.

Other reasons include complications which may cause symptoms afterwards, such as carelessness at operation, inexperience perhaps or an unavoidable accident, injuries or infections at operation, ligation of ducts or of important vessels, leaving behind too large a stump of the cystic duct or a fragment of gallbladder, failure on the part of the surgeon to recognize anomalies in that region, and doing things that should not have been done.

Another cause of subsequent symptoms is the uncomfortable position of the patient during the operation, causing backache or even actual spinal lesions. These patients sometimes return postoperatively with these complaints of backaches and pains of various kinds. Another cause of backache is injury from spinal anesthesia or perhaps maybe due to a

sensitivity to the anesthetic used.

Inadequate preparation for operation is a frequent cause for postoperative symptoms. I make it a practice, except of course, where emergency operation is indicated, to have the patient follow a carefully balanced diet with between-meal feedings for at least a month or two before operation. This provides for adequate biliary drainage, builds up the patient's resistance and gives time for treatment of other conditions (cardiac, renal, pelvic and others) together with eradication of focal infections.

Inadequate postoperative care, especially starting feedings too late, causes many postoperative complications. We have been gradually selling our surgeons the idea of starting feedings immediately or as soon as possible after operation, thus draining the biliary tract and preventing biliary stasis. To do this these feedings should contain adequate fat or oil, should be well balanced and should be given frequently. With the gallbladder removed, the patient needs this frequent drainage or there will be distention of the ducts and perhaps bile backing up into the liver.

Neglect of abdominal wall hygiene may also cause trouble. Patients who are operated upon are often allowed to go home without being told to exercise the abdominal wall, to do anything about the musculature of the abdomen, or they are told to wear a corset or support which further weakens the natural abdominal supports, the muscles.

Prophylaxis, therefore, consists of avoidance of the mistakes that have been mentioned, the use of the frequent feedings and adequate diet, before and after operation and good general hygiene. In spite of all these precautions re-operation may sometimes be necessary to get rid of complications that have developed.

MODERATOR TWISS: *We have another question for Dr. Hanger. Does gallbladder disease influence the electrocardiogram?*

DR. HANGER: Some would say yes. I am more sure of acute pancreatitis. The EKG changes may be definite and start great arguments between the surgeon and cardiologist. Acute pancreatitis can simulate acute coronary disease. In distinguishing between the two, serum amylase is the most important single test. I am sure that the pain, the smooth muscle disturbance in the splanchnic area can produce minor changes. I don't believe it would confuse a good cardiologist.

MODERATOR TWISS: *Dr. Shehadi, if you get no visualization of gallbladder with the double dose of Telepaque, is that evidence of disease?*

DR. SHEHADI: I would consider non-visualization of the gallbladder with two doses of Telepaque as adequate evidence of diseased gallbladder. However, since we now have Cholografin available, we can go one step further and do a third check by means of intravenous cholangiography. We have found at times that even though a double dose of Telepaque has been used with no visualization that Cholografin will bring about visualization whether or not the gallbladder is normal or contains calculi. Dr. Twiss has devised an excellent method whereby he combines Telepaque with the use of paregoric and that has been very helpful, particularly with the double or triple dose. If the gallbladder does not visualize after Telepaque, both with and without paregoric, and after subsequent use of Cholografin we are quite certain that the gallbladder is diseased. To save time and for best evaluation, when the gallbladder does not visualize with Telepaque, we administer Cholografin while the patient is still on the radiographic table, thus completing the examination in a single session. A second dose of Telepaque and a revisit by the patient are no longer necessary.

MODERATOR TWISS: *We have a joint question here. As a matter of fact we have several questions about the patient who has gallstones without symptoms and this one is addressed to Dr. Hanger and to Dr. Patterson: What would you do with a patient over 65 years of age having minimal discomfort, no actual pain but having gallstones as demonstrated by x-ray? Dr. Hanger!*

DR. HANGER: I think the function of the medical man is to keep that patient out of the hands of the surgeon.

MODERATOR TWISS: *There are several questions as to younger patients, under 65, who have stones but no symptoms. How do you feel about that?*

DR. HANGER: That problem comes up rather frequently. I advise younger patients with cholelithiasis to have their gallbladders removed. I think that a stone in the gallbladder is a hazard which can create a clinical emergency at any time. Young people should not have to regulate their lives so as to have a good surgeon always available. The fact that a stone has formed is an index of irritation within the gallbladder, perhaps disturbances which eventually will cause more stones. On the other hand, as the patient gets older and there have been no symptoms, I am very much inclined to take the more conservative attitude.

MODERATOR TWISS: *Dr. Patterson, you have a number of questions*

along the same line. What would you do with the asymptomatic patient having stones in the gallbladder?

DR. PATTERSON: In Dr. Brewer's "Textbook of Surgery" which was standard in many medical schools in 1908, the statement is made that 8 per cent of patients with gallstones need surgery. Of course he was talking about pericholecystic abscesses, complete obstruction of the common duct and similar conditions. Over the last 50 years I think that the 8 per cent has grown almost to 100 per cent. In defense, I would like to report to Dr. Hanger that I recently sent a patient home from the hospital with his gallbladder still *in situ* and full of stones because he was 71 years old. He had had a mild cerebral hemorrhage and had about the worst heart seen in the hospital in a live person in a long time. He is now peacefully at home with his gallbladder.

At times it has been interesting to find a gallbladder full of stones in the course of an operation for something else. The one that first comes to mind was a patient with carcinoma of the cecum. During resection of the right colon we discovered she had a few gallstones. I mentioned this condition to her daughter but not to the patient and it took just about eight months for the gallstones to cause her trouble. The mortality of cholecystectomy per thousand cases is still disturbingly high and to be reckoned with but most of the mortality is associated with complicated cases. The hazard, with modern anesthesia, of removing a gallbladder with stones in a relatively tranquil state is slight, even in the elderly.

I would select these people more by physical type than by age. Obesity is the great hazard for surgery and I would much rather subject to cholecystectomy a patient of 70, with a gallbladder full of stones, but who is thin and in good condition than an extremely obese woman of 50.

MODERATOR TWISS: *Dr. Hanger, can functional disorders of the gastrointestinal tract create liver disease with a three plus cephalin flocculation test?*

DR. HANGER: Yes, patients with ulcerative colitis tend to have focal necrosis in the liver. Whether infected gallbladders can drain into the liver and produce active liver disease is a debatable question, but now and then we do see cases where we suspect that condition. The intestine is full of colon bacilli which produce very toxic substances. However, this material does not seem to be damaging to the normal liver. Whether

abnormal intestinal absorption does produce hepatic damage, I don't know. It is a difficult question to decide.

MODERATOR TWISS: *This is addressed to Dr. Patterson: Suppose you have a patient with congestive heart failure, Grade III, would you operate on him?*

DR. PATTERSON: I think one would certainly try to avoid surgery, at least temporarily. We have had only one case of cholecystectomy for gallbladder disease in the presence of real decompensation. While under observation in the hospital this man developed an acute fulminating cholecystitis. To my surprise and discomfiture his physician asked me to operate on him in this state, and fortunately, he survived the operation. He only survived a few weeks but he died of his heart disease. I certainly would not operate on a patient in the presence of such a hazardous situation unless I was forced into it by acute fulminating cholecystitis.

MODERATOR TWISS: *This is a question for Dr. Andresen: Please comment on the use of Demerol for gallbladder colic.*

DR. ANDRESEN: Personally I very rarely use Demerol. In spite of the fact that morphine has been shown to cause the sphincter of Oddi to contract and acquire a state of spasm, I still use it in gallbladder colic. When combined with a fatty diet, with extra fat, I have found that the sphincter of Oddi will not stay tightly closed and that bile will go down. Sometimes it takes 24 hours but I have seen bile come down while the patient was receiving morphine as often as every four hours to control the pain and meanwhile was having the oily, fat-containing, liquid diet pushed into him, waking him up to feed him every two and one-half or three hours.

MODERATOR TWISS: *Another question for Dr. Andresen: Do you think that asymptomatic cholelithiasis should be treated by surgery?*

DR. ANDRESEN: That is commonly referred to as "the silent gallbladder". Surgeons and internists are always talking about it. The question today, as I look at it, is whether there is some definite indication to operate on this particular patient. As Dr. Patterson pointed out, in the presence of an acute condition operation is indicated. If the patient has no symptoms and is older, I usually set the age at about 60, I prefer not to have him operated on. I have seen such patients go along on a diet such as I have outlined for 15 or 20 years and eventually die of some other condition without any further gallbladder symptoms unless they neg-

lected the diet for a few weeks, did not eat properly, and had another attack of colic. This could again be controlled, and they could go on as before. I believe that a person under 40 with gallstones should be operated on unless there is some definite contraindication. This person may have 30 or 40 years to live with gallstones which could do some damage should some intercurrent disease occur or if the patient is not careful of his diet. So that for the patient under 40 I prefer to have cholecystectomy done, even for silent gallstones.

I recently had a young woman patient 27 years of age whose gallbladder was full of stones. I had her all prepared for operation and in wonderful condition, with no colic in six weeks. I sent her into the hospital for some preliminary studies and found that liver function tests indicated a damaged liver. I sent her right home although I had already arranged for a surgeon to operate on her. That was about four years ago. She has not had another attack of colic, which she had had quite frequently before. She now refuses to be operated on, saying that she feels well.

It is in the group between 40 and 60 years of age that I am on the fence. If the patient 40 or 50 years old has no symptoms and is in good condition I still advise operation. Patients who are not in good condition, I leave alone because I know that in most instances they can be kept comfortable and symptom-free. The patient who has recurrent colic, in spite of everything that is done, should be operated on.

MODERATOR TWISS: *This question is for Dr. Shehadi: If, following intravenous cholography, the gallbladder is not visualized, how is a diseased gallbladder determined?*

DR. SHEHADI: We ran a series of 100 cases last year and followed them through the operating room; every one had a diseased gallbladder.

DR. ANDRESEN: With stone?

DR. SHEHADI: Some with stones and some without stones. The majority had stones but in those without stones the microscopic sections were definitely those of chronic and sometimes chronic recurrent cholecystitis.

MODERATOR TWISS: *Another question for Dr. Shehadi: Above what level of bilirubin, in milligrams, does liver damage preclude adequate filling of the gallbladder by Telepaque?*

DR. SHEHADI: This question is probably either too late or too early for me to answer. I would rather give you an answer about a year from

now. We are trying to re-evaluate this and I would like to skip it if I may.

MODERATOR TWISS: *A final question for Dr. Patterson. Do you feel that there is much use in flushing the common duct for retained common duct stone?*

DR. PATTERSON: I presume this is the treatment suggested by Best of Omaha, the biliary flush. I think Dr. Best is an excellent observer and honest in his opinions. He feels that it is definitely worth while. Of course with the newer x-ray techniques, we hope to be able to establish with certainty the presence of stones and whether or not medical management has or has not gotten rid of them. I think we will know more about this in a few years.

The matter of overlooked calculi is a very sad one. Occasionally stones are seen in the common duct that one believes have been there for many years, even with findings of a normal gallbladder. However, that is very rare.

I would like, as a closing remark to refer Dr. Andresen to a wonderful article by the late Dr. David Cheever of Boston, who was a sort of elder statesman in his later years. He wrote an article called, "The Harmless Gallstone, a Myth". There is a good deal to that notion.

MODERATOR TWISS: *We have one more question for you, Dr. Patterson, relative to surgery: Do you perform cholecystectomy when you find carcinoma of the gallbladder and do you resect part of the liver?*

DR. PATTERSON: Of course the prognosis, in carcinoma of the gallbladder which is obvious at operation, as grossly observed over a period of many years, has been uniformly bad. The idea of taking out just a little pie-shaped piece of liver in the hope that something has been accomplished has not worked out very well. Now that the major hepatectomies are being done with reasonably low mortality, the question arises as to whether or not the right lobe of the liver should be removed in the presence of an obvious carcinoma of the gallbladder. That assumes that the carcinoma has not spread into the area about the pancreas or by metastasis into the pelvis or throughout the abdomen.

I am not yet ready to think that I can do much about carcinoma of the gallbladder except in a preventive way or except, by fortuitously removing the carcinoma of the gallbladder before it really gets well started. About every 20 months we find a small carcinoma in a gallbladder containing stones, that was not recognized by the surgeons and

recognized only by the pathologist. Some of them are as big as a pea, some as big as a ten cent piece and some as big as a nickel and they are real carcinomas. We believe that most of these patients are cured by cholecystectomy. I have never seen carcinoma in a gallbladder that did not have stones in it. Clinically, I know they occur but they are very rare. I don't mean to imply that the possibility of future carcinoma of the gallbladder is a sufficient reason to advise cholecystectomy, because it is a relatively rare disease. The presence of gallstones in the gallbladder does mean that you should advise removal for other good reasons. I don't think patients will be helped very much after it becomes obvious they have a carcinoma of the gallbladder.

MODERATOR TWISS: One final statement by Dr. Andresen, because our time is up.

DR. ANDRESEN: I want to speak about the quotation that Dr. Patterson mentioned in regard to gallstones always being dangerous. The doctor evidently had not had as much experience as I have had in following patients on an adequate diet, with frequent feedings. I would agree, that if the patient with gallstones is not going to get anything to eat but a fat free diet, he ought to be operated on right away.

MODERATOR TWISS: We are very much indebted to our panel for a very instructive and interesting discussion.

A COMMUNICATION TO THE FELLOWS OF THE NEW YORK ACADEMY OF MEDICINE*

THE Council of The New York Academy of Medicine has directed the President to appoint a committee to survey, in searching fashion, the objectives, functions and activities of the Academy as they exist today. The Survey Committee is also charged with the task of making recommendations concerning future procedure and policies, as well as effective and practical means for executing them.

Such a formal survey has never before been attempted. Some of the more cogent reasons for undertaking it at this time are: first, the organizational and corporate growth of the Academy since its founding one hundred and ten years ago; second, the expansion of its activities, both in medical and adjacent fields; third, a desire to retain the position of leadership which it has attained, not only in the local community, but throughout the nation and abroad. In each of these reasons are implied certain responsibilities which must be met, thoughtfully and with foresight. But an even stronger motive for self-examination is afforded by the altered scene in which the Academy operates. Numerous factors have served to bring about new viewpoints, both lay and professional, toward medicine in the modern world. Among these may be mentioned the impact of insurance, of medical care in industry, of labor union participation, of the educational experiments and programs in universities and hospitals, the increase in the number of societies devoted to medical specialties, the rise of voluntary health agencies and the growing part played by governmental public health services. There is a general awareness of the importance of basic research. The interplay of professional and lay journalism, as well as the wide potential influence of radio and television, cannot be ignored. The Academy, in order to meet its obligations and render the greatest possible service, must adapt itself to a changing environment.

* This communication appeared first in the October, 1957 number of the Bulletin (p. 663). Because of its importance it is deemed advisable to publish it a second time. *Editor.*

In compliance with the directive of the Council, your President has appointed the following Fellows as a Survey Committee, under the general chairmanship of Dr. William Barclay Parsons, and each will act as chairman of a subcommittee to study one phase of the activities of the Academy:

Administration:	Marcus D. Kogel
Building & Plant:	Condict W. Cutler, Jr.
Bulletin:	Louis J. Soffer
Finance:	Henry N. Pratt
Library:	George Rosen
Medical Education:	Dickinson W. Richards, Jr.
Medical Information:	John H. Garlock
Public Health:	Duncan W. Clark

This group and its Chairman, Dr. Parsons, constitute an Executive Committee. Comments, critical or otherwise, are earnestly solicited from the Fellows concerning any aspect of the activities or operation of the Academy. Such communications should be addressed to Dr. Parsons or to one of the subcommittee Chairmen to whose particular field of study the comments may appropriately apply; these may be sent to the Academy address.

The Survey Committee will submit its findings and recommendations to the Council for approval and action. It is anticipated that the final report will be ready for publication during the coming year.

It is the sincere hope of the Officers and Council that the entire Fellowship will contribute of its experience and thinking to this project, so that the usefulness of the Academy, to its Fellows, to the medical profession at large and to the community, may be increased.

Robert L. Levy	William Barclay Parsons	Howard Reid Craig
President	*Chairman, Survey Committee*	*Director*

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

Presented at the Meeting, January 24, 1957, at The New York Academy of Medicine

The Nature and Origin of Fibrinoid: Morphological, Histochemical and Histoenzymatic Studies

HENRY Z. MOVAT†

Department of Pathology, Memorial Center for Cancer and Allied Diseases*

Much controversy exists concerning the nature and origin of fibrinoid. The various theories derive it from collagen, ground substance, nucleoprotein or fibrin. The following observations were made on human and experimental fibrinoid:

Experimentally, fibrinoid was produced by a number of methods all causing injury to connective tissue. Mechanical injury to the skin of rabbits resulted following incision, chemical injury following injection of trypsin, and radiation injury after insertion of radon seeds or x-radiation. Allergic injury of both skin and joint was produced by eliciting the Arthus phenomenon. Lesions of systemic hypersensitivity with fibrinoid were produced with one or more massive intravenous doses of foreign protein. Fibrinoid in a number of lesions from the "diffuse collagen diseases," arteriosclerosis, placentae and peptic ulcers constituted the human material of our studies. Morphologic and histochemical studies were carried out on the fibrinoid of both the experimental and human lesions.

The experimental lesions were studied at serial time intervals. The earliest change, in all types of lesions, was an acute inflammation in which varying amounts of fibrin could be demonstrated. At all stages, fibrin with other plasma constituents had conglomerated and inspissated, thus having all the characteristics of fibrinoid. Fibrinoid was acidophilic (eosinophilic), homogeneous and refractile, and gave staining reactions similar to fibrin. It stained red with trichrome or azan, dark blue with phosphotungstic acid hematoxylin, and red-purple with PAS. With the aid of histochemical methods, the amino acids tyrosine, tryptophane, cysteine and cystine could be demonstrated in both reticular fibrin and homogeneous fibrinoid. Incubation of frozen-substituted or absolute alcohol-fixed sections with trypsin (Nutritional Biochemicals) resulted in digestion of both fibrin and fibrinoid, while collagen remained unchanged. Acid mucopolysaccharides were decreased in the earliest exudative lesions and increased as regeneration and repair commenced, and young connective tissue was laid down.[1, 2] Fibrinoid was embedded in this material. Following incubation with testicular hyaluronidase (Wyeth) the staining of acid mucopolysaccharide was inhibited or diminished, but the fibrinoid remained unchanged.

In the human lesions, all the various stages of fibrinoid formation could be traced from delicate threads of fibrin to bands, clumps, and large masses which showed all the morphologic and tinctorial characteristics of fibrinoid described above.

* This work was carried out between 1953 and 1956 in the Department of Pathology, Queen's University, Kingston, Canada.

† Now associated with University of Toronto, The Banting Institute, Toronto, Canada.

Histochemically, fibrin and fibrinoid gave all the reactions found in the experimental fibrinoid. A hematoxylinophilia was at times associated with fibrinoid in disseminated lupus, but it was found occasionally also in rheumatoid arthritis and periarteritis nodosa. The fibrinoid always gave a positive Feulgen reaction. Possibly the most significant finding was the digestion of fibrinoid with fibrinolysin (Parke, Davis) in frozen-substituted or alcohol-fixed tissues. Trypsin had a similar effect. Collagenase (Burroughs, Wellcome & Co.) treatment caused loss of staining of collagen but did not affect the fibrinoid.

Acid mucopolysaccharides could be demonstrated only in advanced lesions showing fibrinoid. The reason for this is that they are associated with repair, i.e., formation of young connective tissue.[1-4]

The demonstration of increased amounts of mucopolysaccharides in association with fibrinoid has led some investigators[5] to conclude that fibrinoid is derived from a precipitation of mucopolysaccharides. However, in the earliest exudative lesions they are diminished or at least not demonstrable by histochemical methods.[1, 2]

From these studies there is ample morphologic evidence that fibrinoid derives from conglomeration and inspissation of plasma, particularly fibrin. Histochemical evidence supports this view: the amino acids which can be demonstrated histochemically in fibrinoid are present in fibrin and other plasma proteins, but are absent or in low concentration in connective tissue. In alcohol-fixed tissue, fibrinoid is digested by trypsin and fibrinolysin, whereas collagenase and hyaluronidase alter only the connective tissue, but not the fibrinoid.

It was concluded from these studies that fibrinoid derives from fibrin which is exuded during the course of a fibrinous or serofibrinous inflammation.[6, 7] There is little evidence that fibrinoid derives from collagen or connective tissue ground substance. Degenerating elements of connective tissue, i.e., collagen and ground substance, and also nuclear material and various plasma constituents, may be intimately associated with fibrin in the formation of fibrinoid, but fibrin is the only constant component. Without fibrin there can be no formation of fibrinoid, or, at least, of the substance which Neumann (the originator of the term) has defined as an acidophilic, homogeneous and refractile material with the staining characteristics of fibrin.

REFERENCES

1. Movat, H. Z. Experimentelle Studien über die allergische Gewebsreaktion, *Beitr. path. Anat. 116:* 238-48, 1956.
2. More, R. H. and Movat, H. Z. Studies on injury reactivity and repair of connective tissue. I X. To be published.
3. Movat, H. Z. and More, R. H. Morphological and histochemical studies on the development and progression of arteriosclerosis (abstract), *Circulation 12:* 484, 1955.
4. Haust, D. M., Movat, H. Z. and More, R. H. The role of fibrin thrombi in the genesis of the common white plaque in arteriosclerosis (abstract), *Circulation 14:* 483, 1956.
5. Altshuler, C. H. and Angevine, M. Histochemical studies on the pathogenesis of fibrinoid. *Amer. J. Path. 25:* 1061-77, 1949.
6. Marchand, F. Zur Kenntnis der fibrinösen Exsudation bei Entzündung. *Virchow's Archiv 145:* 279-316, 1896.
7. Meyer, W. W. Interstitielle fibrinöse Entzündung im Formenkreis dysorischer Vorgänge, *Klin. Wschr. 28:* 697-703, 1950.

DISCUSSION

LOUIS ODESSKY: I would like to know exactly when does fibrin become fibrinoid when you see it microscopically. When can you say you are looking at fibrin and when at fibrinoid?

ALFRED ANGRIST: Will this presentation necessarily rule out the active participation of fibrinogen in the formation of fibrin by heparin and other acidic polysaccharides, etc., suggested by the work of Altshuler, Thomas, and others?

SIGMUND L. WILENS: Dr. Cooper I know is interested in this subject; has he anything he would like to say?

NORMAN S. COOPER: I would like to congratulate the author on an excellently presented paper. I think there has been considerable accumulating evidence that the term "fibrinoid" is a red (or Orange G) herring and this material certainly supports the concept that it is really old fibrin.

HENRY Z. MOVAT: The first question I am afraid I cannot answer fully. We

were taught in medical school to call fibrin threads and meshworks with definite staining characteristics. Fibrinoid on the other hand is defined as clumps and bands of an acidophilic and refractile material with the staining properties of fibrin.

Two years ago at Queen's University in Canada, seeing the pathology class slides showing pericarditis in a case of lupus (representing an example of fibrinoid) and one of uremic pericarditis (used as an example of fibrinous exudate), I covered up the labels and showed the slide to one of our demonstrators. He diagnosed both as fibrinous pericarditis, although he taught the students that in the case of lupus, the material was "fibrinoid". Transition between fibrin and fibrinoid occurs frequently as demonstrated in the slides which I presented.

In regard to the question by Dr. Angrist, I would like to say that the role of acid mucopolysaccharides in the formation of fibrinoid as suggested first by Altshuler and Angevine has not as yet been definitely established. Dr. Angevine seems to believe now that fibrinoid derives from some sort of plasma components, as pointed out by him some two years ago when I presented the preliminaries of this work. He still believes, however, in the precipitating role played by the mucopolysaccharides as suggested in their original work. In our studies dealing with experimental fibrinoid we could not demonstrate an increase but rather a decrease of acid mucopolysaccharides in the early exudative lesion. Tissues rich in polysaccharides showed a swelling or mucinous edema. At later stages an increase of these substances could be demonstrated in connection with early repair. I am inclined to think that depolymerization of polysaccharides is followed by an increased permeability of the ground substance, thus facilitating the exudation of plasma proteins.

SIGMUND L. WILENS: What is the purpose of retaining the term "fibrinoid"? Do you think it should be discarded, and one should just use fibrin?

HENRY Z. MOVAT: No, I do not believe it should be discarded. People will use the term just as they will continue using the term "collagen diseases" which some people tried to discard but without success. Fibrinoid is not fibrin after all; it is a physically altered fibrin.

SIGMUND L. WILENS: You think then there is sufficient reason for retaining the term?

HENRY Z. MOVAT: Yes, I do.

Recent Advances in Enzymatic Histochemistry (Abstract)*

MAX WACHSTEIN and ELIZABETH MEISEL

Department of Pathology, St. Catherine's Hospital, Brooklyn, N. Y.

Of the multitude of enzymes known, only relatively few hydrolytic and oxidative ones can be visualized by histochemical techniques at present. Those demonstrable are not necessarily the most important ones, but have been developed mostly because of fortuitous circumstances.

The biochemist, in studying enzymatic reactions in tissue extracts, can use all methods of modern chemistry for their recognition and measurement, as, for instance, color reactions, gas analysis, etc. The histochemist is almost exclusively limited to the use of color reactions. The biochemist destroys the tissue structure and prepares liquid extracts in which biochemical reactions can be studied under optimal conditions. The histochemist in contrast must preserve the integrity of the tissue and considers as a minimal goal the correct localization of enzymatic activity at a cellular and as a maximal on a subcellular level. He is, therefore, confronted with the problem of adequate tissue preparation for best results.

For this purpose various methods can be employed. A) Frozen sections from fresh unfixed material cut either on a conventional or a Sartorius freezing microtome[1] or in a Linderstrom-Lang type cryostat at low temperature.[2] B) Paraffin sections from frozen-dried material.[3] C) Frozen sections of tissues fixed in neutral cold formalin. D) Paraffin sections of tissue fixed in cold acetone followed by routine dehydration techniques.[4-6]

It is obvious that one of the products formed by enzymatic action must be precipitated in insoluble form at the exact place of its origin. This substance must be itself colored or be convertible into a colored product. The following procedures are at present used for this purpose. A) The conversion of products of enzymatic hydrolysis into compounds of lead, cobalt or copper which can be visualized as dark sulfides. This principle is used in procedures for demonstration of various phosphatases, choline esterase,[4-6] carbon-anhydrase,[7] etc. B) Coupling reactions in which diazonium salts will form brilliant azodyes with the products of enzymatic hydrolysis. This technique is finding an ever-increasing application and is used for the demonstration of alkaline and acid phosphate, esterases,[4-6] glucuronidase,[8] etc. C) The formation of insoluble colored products either by the action of oxidative or reducing enzymes.[4-6] Various dehydrogenases can be demonstrated by the formation of insoluble tetrazolium salts or insoluble tellurium.[9] D) The formation of an insoluble substance visualized by a specific staining reaction as in the case of phosphorylase.[10]

The question of exact localization of enzymatic activity is far from settled. Most investigators agree that in the Gomori technique for alkaline phosphatase a nuclear reaction is spurious and does not represent a true picture of enzymatic localization. Holt[11] in a thorough study has recently applied improved techniques in an attempt to establish localization of esterase on a subcellular level. He found this enzyme in discrete bodies in the cytoplasm of renal and hepatic cells in the rat. This however, does not agree with findings established by differential centrifugation, since esterase is connected with the microsome fraction and not with larger structures.[12]

Closely related to the problem of exact

* Supported by Research Grant A-688, the National Institutes of Health, United States Public Health Service.

localization is the problem of choosing the correct tissue preparation. For some enzymes, for instance, succinic dehydrogenase or glucose-6-phosphatase, unfixed frozen sections or frozen-dried sections must be used since any type of fixation destroys these enzymes. Occasionally activity is differentially inactivated by fixatives. Adenosinetriphosphatase activity in striated muscle is completely abolished by formalin fixation, but staining of vascular endothelium is not diminished.[13]

In a recent study, Nachlas, Prinn and Seligman[14] have shown that large portions of some enzymes diffuse into the surrounding medium from fresh frozen sections while previous fixation of the material leads to a greater retention of enzyme activity. There are, however, great quantitative differences between various enzymes tested. Acetone fixation followed by conventional tissue preparation and paraffin embedding causes considerable loss of enzymatic activity.[15]

From the point of view of histochemical localization, quantitative differences appear less important than shifts in cellular distribution of enzymes. Does the better definition of structures often seen in formalin fixed, as compared to unfixed frozen sections, necessarily reflect the true state as it occurs in the living cell? Considerable differences in staining patterns of alkaline phosphatase can easily be detected in fresh and formalin fixed kidney sections.[16] In unfixed sections the cytoplasm stains diffusely while in fixed sections staining occurs preferentially in brushborders. In fixed sections from the rat kidney stained for phosphatase or 5-nucleotidase at pH 7.2, activity of the proximal convolutions is localized moreover in small bodies not unlike those described by Holt in his preparation of esterase.

The histochemical specificity of some staining reactions can be more clearly delineated by the inclusion of activators and inhibitors in the incubation mixtures. Thus cholinesterase can be separated from nonspecific esterases by its sensitivity to eserine.

From a practical point of view it is important to realize that in biopsies from human sources and in tissues from animals, enzymes are apparently more stable than is usually assumed and that histochemical distribution patterns in many instances remain unchanged for comparatively long periods of time. On the other hand, postmortem material often gives disappointing results. The influence of agonal changes must be further evaluated. Differences among various species must also be taken into account. While some reactions are limited to one or several species, others occur in certain tissues of all mammalian organs so far examined. Alkaline phosphatase and succinic dehydrogenase activity, for instance, are found without exception, in the proximal convoluted tubules of the kidney.

In this paper only a few examples of enzymatic staining reactions can be given. Succinic dehydrogenase is demonstrable in many organs.[17] The heart gives regularly a very strong reaction. The tongue shows a strong reaction closely resembling that of the heart, while the skeletal muscles show great variations in individual fibers.[18] The distribution of reduced tetrazolium particles indicating enzymatic activity in the muscle and heart resembles closely that of stainable mitochondria. In myocardial infarction, a decrease of enzymatic activity is noticed occasionally within three hours after the onset of clinical symptoms.[19] This time relation may, however, be incorrect since, in experimental infarction in the dog, diminution of activity becomes noticeable only after 12 to 15 hours.[20] Two other histochemical findings in the heart deserve mention. In the rat, the intercalated discs give a positive staining reaction when pyridoxal phosphate at pH 9[21] or muscle adenylic acid at pH 7.2 is used as substrate.[22] This is of particular interest in view of findings with the electron microscope suggesting that intercalated discs interrupt the muscle fibers and that, therefore, a myocardial syncytium does not exist.[23] The conductive system of the heart is characterized by the presence of true acetylcholinesterase. This specific enzyme is not present in the myocardium.[24]

Eserin-sensitive acetylcholinesterase can also be demonstrated in the motor endplates of striated muscle. This staining reaction can be reversibly influenced by

anticholinergic drugs[25] and disappears after nerve dissection.[26]

In the kidney, a number of enzymatic reactions can be localized in various portions of the nephron.[16] It is not surprising that the most consistent staining reactions for various enzymes should be given by the proximal convoluted tubules in which most of the work load of the kidney is performed. Some enzymes are also found in the collecting tubules, for instance, DPN-diaphorase, esterase and glucuronidase. DPN-diaphorase,[27] one of the enzymes involved in the tricarboxylic acid cycle, can also be visualized in thin limbs of Henle's loops and in cells composing the glomeruli.

In experimentally induced renal necrosis, enzymatic changes occur at a faster rate following the actions of various poisons as, for instance, mercury or DL-serine, than following the ligation of the renal artery.[28] Of various enzymes tested, succinic dehydrogenase proved to be the most sensitive. After the administration of a toxic dose of mercuhydrin it disappeared within three to six hours from the proximal convoluted tubules, while even 24 hours after arterial ligation residual enzymatic activity was still present. Regenerating tubules regain their enzymes only slowly. First to reappear is succinic dehydrogenase.[16]

Not only complete necrosis, but less drastic changes influence the enzymatic staining of renal tubules. Following experimental ureteral ligation, alkaline phosphatase[29] as well as other enzymes[16] disappear from the hydronephrotic kidney. In the experimental Masugi type of nephritis, various enzymes diminish rather rapidly in renal tubules.[30]

Glucose-6-phosphatase, one of the most important enzymes involved in intermediary carbohydrate metabolism, can easily be demonstrated in liver sections.[31] Its diminution in some cases of glycogen storage disease has been reported.[32] In view of the increase of serum alkaline phosphatase in liver disease, the stainability of bile capillaries with the technique for alkaline phosphatase is of great interest. However, these structures are more regularly demonstrable when adenosine triphosphate at pH 7.2 is used as substrate.[33] In surgical biopsies of patients with obstructive jaundice and in livers of animals with experimental biliary obstruction, some bile canaliculi show marked dilatation; others show reduced enzymatic activity especially after longer lasting obstruction. Necrotic cells[34] as well as liver cells with carcinomatous transformation in ethionine-induced hepatoma show no reaction of bile canaliculi.[22]

Recently the possibility of visualizing the activity of phosphorylase in tissue sections has been reported. The effect of this enzyme can be recognized by the deposition of newly formed glycogen.[10] It can be demonstrated particularly well in striated muscle.[35]

It has been suggested that we make use of the abundance of acid phosphatase in the prostate for the identification of tumors of prostatic origin.[36, 37] In fresh or formalin-fixed frozen sections from carcinoma of the prostate a large amount of stainable acid phosphatase is demonstrated in most cases.

With the problem posed by the action of Diamox (sodium acetazoleamide) a technique for the histochemical demonstration of carbonanhydrase[7, 38] could be expected to help in evaluating the effect of this carbonanhydrase inhibitor. In our hands, good results with this method were only obtained in the rat stomach in which a remarkable staining reaction was observed in the parietal cells. This was not influenced by Diamox administration *in vivo* or *in vitro* unless enormous amounts of the drug were added to the incubation mixture.[39]

In closing, it might be of interest to refer to an observation first reported ten years ago before this Society. It could be shown that the mature leukocytes in slides from patients with chronic myeloid leukemia exhibited little or no reaction for alkaline phosphatase. In contrast, the leukocytes of patients with a myeloid reaction or with infectious leukocytosis showed a very strong reaction.[40] This observation has only recently been confirmed by various investigators[41, 42] and can be used as a practical method for the differentiation of a true myeloid leukemia from a myeloid reaction.

While much basic research will have to be done, histochemistry in general and enzymatic histochemistry in particular will undoubtedly be of increasing importance in general and experimental pathology.

DISCUSSION

ANNA GOLDFEDER: I wish to comment on Dr. Wachstein's remark that chemists are overly concerned with the freezing of tissues immediately after their removal from the animal organism for enzymatic reaction studies.

There is justification for freezing the respective tissues for metabolic investigations, not only immediately after their removal from the organism, but even for freezing them while still *in situ*. For example, phosphocreatine in the brain tissue was first detected when liquid air was poured on the brain of the living animal. This holds true for other intermediary metabolites which are very labile.

Activity of certain enzymes may proceed in excised tissues as long as the enzymes are provided with the required substrates which are preserved in the "reservoir" of cellular constituents. Dr. Wachstein's observations of enzymatic activity in tissues after they have been removed from the intact animal after some length of time may be explained on this basis.

MAX WACHSTEIN: Dr. Goldfeder is, of course, entirely correct. For many investigations involving intermediary metabolism tissues must be frozen immediately. However, those enzymes which at present can be demonstrated histochemically are considerably more resistant to higher temperature and postmortem changes than has been assumed previously.

SIGMUND L. WILENS: I think the lack of discussion is not due to the fact that we are not interested and impressed by the material you presented, Dr. Wachstein, but is due rather to the fact that few of us feel qualified to discuss the problem intelligently. I think many of us are old-fashioned tissue readers and are used to the traditional methods of examination of tissues by old-fashioned techniques. I think some of us wonder if at the present time you can give us any examples of a lesion which we might fail to recognize by the ordinary methods and which this relatively new science of enzymatic histochemistry would reveal.

MAX WACHSTEIN: As a tissue pathologist, I believe that ordinary staining techniques will almost invariably permit a satisfactory evaluation of the underlying pathology. For instance, a prostatic carcinoma can be recognized without resorting to specific staining for acid phosphatase, although occasionally this might help to identify the origin of a metastatic lesion.

Commenting on the previous presentation by Dr. Movat, one might say that fibrinoid is usually recognized by an ordinary hematoxylin and eosin stain, but that the use of histochemical methods can contribute to the understanding of the fundamental nature of abnormal tissue reactions. The application of enzymatic histochemistry to the kidney certainly must impress all those who are only accustomed to use the ordinary staining techniques. Changes which occur in the kidney under experimental conditions are very impressive. How far the application of these techniques will advance the practice of pathology is, of course, entirely undecided. In closing, may I just point out again that the use of the stain for alkaline phosphatase is very useful for the differentiation of chronic myeloid leukemia from leukemoid states.

REFERENCES

1. Wachstein, M. and Meisel, E. Thin sections from unfixed tissues for histochemical staining, *Stain Technol. 28:* 135-39, 1953.
2. Coons, A. H., Leduc, E. H. and Kaplan, M. H. Localization of antigen in tissue cells. VI, *J. exp. Med. 93:* 173-88, 1951.
3. Burstone, M. S. A method of freeze-drying and its use in histochemistry and pathology, *J. nat. Cancer Inst. 17:* 49-56, 1956.
4. Gomori, G. *Microscopic histochemistry; principle and practice.* Chicago, Univ. of Chicago Press, 1952, p. 137-221.
5. Pearse, A. G. E. *Histochemistry; theoretical and applied.* Boston, Little, Brown and Company, 1953, p. 215-313.
6. Lillie, R. D. *Histopathologic technic and practical histochemistry.* New York, The Blakiston Company, 1954, p. 199-236.
7. Kurata, Y. Histochemical demonstration of carbonic anhydrase activity, *Stain Technol. 28:* 231-33, 1953.
8. Seligman, A. M., Tsou, K. C., Rutenberg, S. H. and Cohen, R. B. Histochemical demonstration of *B*-d-glucuronidase with a synthetic substrate, *J. Histochem. Cytochem. 2:* 209-29, 1954.
9. Wachstein, M. Reduction of potassium tellurite by living tissues, *Proc. Soc. exp. Biol. Med. 72:* 175-78, 1949.
10. Takeuchi, T. and Kuriaki, H. Histochemical detection of phosphorylase in animal tissues, *J. Histochem. Cytochem. 3:* 153-60, 1955.
11. Holt, S. J. The value of fundamental studies of staining reactions in enzyme histochemistry, with reference to indoxyl methods for estera-

ses, *J. Histochem. Cytochem. 4:* 541-52, 1956.
12. Underhay, E., Holt, S. J., Beaufay, H. and de Duve, C. Intracellular localization of esterase in rat liver, *J. biophys. biochem. Cytol. 2:* 635-37, 1956.
13. Wachstein, M. and Meisel, E. Histochemistry of substrate specific phosphatases at a physiological pH (abstract), *J. Histochem. Cytochem. 4:* 424-25, 1956.
14. Nachlas, M. M., Prinn, W. and Seligman, A. M. Quantitative estimation of lyo- and desmoenzymes in tissue sections with and without fixation, *J. biophys. biochem. Cytol. 2:* 487-502, 1956.
15. Seligman, A. M., Chauncey, H. H. and Nachlas, M. M. Effect of formalin fixation on the activity of five enzymes of rat liver, *Stain Technol. 26:* 19-23, 1951.
16. Wachstein, M. Histochemical staining reactions of the normally functioning and abnormal kidney, *J. Histochem. Cytochem. 3:* 246-70, 1955.
17. Rutenberg, A. M., Wolman, M. and Seligman, A. M. Comparative distribution of succinic dehydrogenase in six mammals and modification in the histochemical technique, *J. Histochem. Cytochem. 1:* 66-81, 1953.
18. Wachstein, M. and Meisel, E. The distribution of histochemically demonstrable succinic dehydrogenase and of mitochondria in tongue and skeletal muscles, *J. biophys. biochem. Cytol. 1:* 483-88, 1955.
19. Wachstein, M. and Meisel, E. Succinic dehydrogenase activity in myocardial infarction and in induced myocardial necrosis, *Amer. J. Path. 31:* 353-65, 1955.
20. Kent, S. P. and Diseker, M. Early myocardial ischemia, *Lab. Invest. 4:* 398-405, 1955.
21. Bourne, G. H. The histochemical dephosphorylation of riboflavin phosphate (flavin mononucleotide) and pyridoxal phosphate (Co-decarboxylase), *Quart. J. Micros. Sci. 95:* 359-69, 1954.
22. Wachstein, M. and Meisel, E. Unpublished observations.
23. Van Breemen, V. L. Intercalated discs in heart muscle studied with the electron microscope, *Anat. Rec. 117:* 49-56, 1953.
24. Carbonell, L. M. Esterases of the conductive system of the heart, *J. Histochem. Cytochem. 4:* 87-95, 1956.
25. Denz, F. A. Cholinesterase inhibition at myoneural junction, *Brit. J. exp. Path. 35:* 459-71, 1954.
26. Snell, R. S. and McIntrye, N. Changes in the histochemical appearance of cholinesterase at the motor end plate following denervation. *Brit. J. exp. Path. 37:* 44-48, 1956.
27. Farber, E., Sternberg, W. H. and Dunlap, C. F. Histochemical localization of specific oxidative enzymes. I. Tetrazolium stains for diphosphopyridine nucleotide diaphorase and triphosphopyridine nucleotide diaphorase, *J. Histochem. Cytochem. 4:* 254-65, 1956.
28. Wachstein, M. and Meisel, E. A comparative study of enzymatic staining reactions in the rat kidney with necrobiosis induced by ischemia and nephrotoxic agents (mercuhydrin and D-L serine), *J. Histochem. Cytochem.* in press.
29. Wilmer, H. A. The disappearance of phosphatase from the hydronephrotic kidney, *J. exp. Med. 78:* 225-30, 1943.
30. Wachstein, M. and Lange, K. Morphology and histochemistry of experimental nephritis in the rabbit with and without cortisone (abstract), *Fed. Proc. 16:* 375-76, 1957.
31. Chiquoine, A. D. The distribution of glucose-6-phosphatase in the liver and kidney of the mouse, *J. Histochem. Cytochem. 1:* 429-35, 1953.
32. Cori, G. T. Glycogen structure and enzyme deficiencies in glycogen storage disease, *Harvey Lectures 48:* 145-71, 1953.
33. Wachstein, M. and Meisel, E. Histochemistry of hepatic phosphatases at a physiological pH with special reference to the demonstration of bile canaliculi, *Amer. J. clin. Path. 27:* 13-23, 1957.
34. Wachstein, M. and Meisel, E. The histochemistry of adenosinetriphosphatase and 5- nucleotidase in the liver with biliary obstruction and cellular necrosis (abstract), *Amer. J. Path. 32:* 635, 1956.
35. Takeuchi, T., Higashi, K. and Watanuki, S. Distribution of amylophosphorylase in various tissues of human and mammalian organs, *J. Histochem. Cytochem. 3:* 485-91, 1955.
36. Changus, G. W. Identification of metastatic prostatic carcinoma (abstract), *Fed. Proc. 11:* 410-11, 1952.
37. Reiner, L., Rutenberg, A. M. and Seligman, A. M. Acid phosphatase activity of human tumors (abstract), *J. Histochem. Cytochem. 3:* 395-96, 1955.
38. Goebel, A. and Puchtler, H. Zur Darstellung der Carbonanhydrase im histologischen Schnitt, *Naturwiss. 41:* 531-32, 1954.
39. Puchtler, H. and Raminger, K. Einfluss von Diamox auf die histochemisch nachweisbare Carbonanhydrase, *Naturwiss. 42:* 297-98, 1955.
40. Wachstein, M. Alkaline phosphatase activity in normal and abnormal human blood and bone marrow cells, *J. Lab. clin. Med. 31:* 1-17, 1946.
41. Frost, H. Alkaline phosphatase activity in neutrophils as studied by a simple slide test (abstract), *J. Lab. clin. Med. 46:* 817-18, 1955.
42. Wiltshaw, E. and Moloney, W. C. Histochemical and biochemical studies on leukocytic alkaline phosphatase activity, *Blood 10:* 1120-31, 1955.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

Presented at the Meeting on February 28, 1957 at The New York Academy of Medicine

How Specific Should a Tumor Antigen Be?

MAURICE M. RAPPORT, Ph.D.

Section of Immunology, Sloan-Kettering Institute for Cancer Research, New York

Studies of the distribution of antigenic constituents of neoplastic tissues using heterologous antibody as a specific reagent must be clearly distinguished from studies of host response to such constituents. Analysis of tissues with antibody reagents is being pursued by many groups using such diverse methods as conventional *in vitro* precipitation and complement-fixation; some newer modifications such as gel diffusion and staining with fluorescent antibody; and provocation of anaphylaxis in guinea pigs. These analytical methods are not capable of *proving* that an antigen is "specific", that is, unique for a certain tissue. What they are able to show is whether a difference exists between the quantity of some constituent in one tissue and the quantity in other tissues. When these differences are sufficiently large, they are exploitable in several ways. To make use of these differences, we must be able to determine them with both precision and accuracy. For this reason, *in vivo* methods such as anaphylaxis, or histologic methods using labelled antibody, suffer from much greater limitations than *in vitro* techniques.

The question "How Specific Should a Tumor Antigen Be?" attempts to focus attention on the fact that "specific" cannot be defined by analysis. It is equivalent to asking "How large should a quantitative difference be before we call it qualitative?" Since this question has no answer, the proper yardstick by which to judge analytical studies of tumor antigens is "How much of a difference do you find, and with what precision and accuracy can you determine it?" The problem of absolute specificity can be resolved only by isolation and characterization of the substances which react with the antibody reagent.

DISCUSSION

SIGMUND L. WILENS: Dr. Rapport has asked a provocative question and provided some provocative answers. I wonder if there is anyone in the audience who would like to discuss the matter, or ask any questions. Since we are merely pathologists, not capable of evaluating some of the material which Dr. Rapport has presented to us, I have asked Dr. Chandler Stetson to be our discussor.

CHANDLER A. STETSON, Jr.: I was delighted when Dr. Wilens asked me to discuss this paper. Both the title and the presentation were fascinating, and I think this is the first time I have heard this question raised in just this provocative and detailed fashion. I would like to discuss it from the point of view of an interested, non-expert bystander.

I think Dr. Rapport did well by defining terms, or perhaps by suggesting the redefining of some of our terms. As long as the science of immunology dealt primarily with bacteria and bacterial antigens, we

were inclined to think in a rather circumscribed way of what "antigen" or "antibody" should properly mean. Perhaps now the term "antigen" should, as Dr. Rapport suggests, be re-defined as "something which will react with an antibody". A critic of this point of view would certainly insist on drawing a line somewhere, and excluding non-specific chemical reactants, but I suppose that would be quibbling.

I think that Dr. Rapport's general line of investigation aimed toward diagnosis of tumors is an extremely intriguing and I think promising one. It has been intriguing to people for a long time, of course, but I think perhaps it does hold more promise now than it did 20 years ago, partly because our ideas about specificity are becoming more sophisticated, as Dr. Rapport pointed out. His notion that there is perhaps no such thing as absolute qualitative specificity in an antigen-antibody system is exciting, and I wonder whether in the future there may be two kinds of immunology, one in which there is qualitative specificity, and one in which it is only quantitative, analogous to the heterograft-homograft system.

The other main objective of this sort of investigation on tumor antigens, as Dr. Rapport mentioned, is to get some notion of new antigens, or antigens in detectable quantities in tumor cells not present in normal cells, and this sort of information may give us some insight into the mechanism of oncogenesis. It seems to me this is at least as important as the other line of investigation, and as Dr. Rapport indicated, has already provided some fascinating leads and clues.

Abnormal Antigens in Multiple Myeloma (Abstract)

LEONHARD KORNGOLD

Sloan-Kettering Institute for Cancer Research, New York

Most patients who have multiple myeloma synthesize large amounts of electrophoretically homogeneous serum proteins. These proteins may have electrophoretic mobilities ranging from that of very slow gamma globulin to that of alpha-2 globulin. The urines of approximately 50 per cent of these patients will contain Bence Jones proteins, i.e., proteins of low molecular weight which precipitate in acid medium at 60° C and redissolve on boiling. For the last few years we have studied the antigenic properties of both these serum and urinary proteins and compared them with normal gamma globulins. This study was facilitated by the introduction of the Ouchterlony technique[1] in which antigens and antibodies diffuse towards each other through an agar medium. Lines of specific precipitate form in the region of optimal proportions for each antigen-antibody system. When three reservoirs are arranged in a triangle and the same antigen is placed in two and antibody in the third, the lines coalesce. If one reservoir contains the immunizing antigen and the other a closely related cross-reacting antigen, a spur forms at the site of fusion of the lines.[2] In our work, antisera were prepared against normal human gamma globulin and multiple myeloma proteins of three patients. The anti-gamma globulin sera were exhaustively absorbed with normal human serum albumin and, in later studies, also with a beta globulin fraction. These absorbed antisera formed one line only with normal gamma-2 globulin and cross-reacted with all purified multiple myeloma serum proteins regardless of their electrophoretic mobility, which ranged from gamma-2 globulin to alpha-2 globulin. The spurs that are formed between the lines of the gamma globulin and the mul-

tiple myeloma proteins indicate that the latter lack some antigenic groupings of normal gamma globulin.[2, 3] We have fractionated normal gamma globulin by various methods into components with different electrophoretic mobilities, but were unable to differentiate these components from the unfractionated gamma globulin. Multiple myeloma proteins from different patients are antigenically dissimilar, and we have shown that they can be placed in three main antigenic groups.[2] There is no correlation between antigenic grouping and electrophoretic mobility. A study comprising over 100 multiple myeloma sera shows that approximately 45 per cent belong to group I, which is antigenically closely related to normal gamma globulin; 35 per cent belong to group III, which is antigenically most abnormal, and 20 per cent belong to group II. All beta globulins and one alpha-2 globulin belong to group III, but this group also contains proteins with mobilities of gamma-2 globulin. At present we are trying to correlate the severity of the disease and the antigenic group of the patient's abnormal serum protein.

The antisera against purified multiple myeloma globulins cross-react with the proteins from other patients and with normal gamma globulin.[3] However, the homologous globulin contains antigenic groupings that are absent from all normal serum proteins or the proteins from other patients' sera. Such an anti-multiple myeloma serum, after exhaustive absorption with normal serum proteins, is completely patient-specific and cannot be used for diagnostic purposes.

These immunologic data are compatible with the hypothesis that myeloma globulins are antigenically abnormal gamma globulins; they lack some normal antigenic groupings and possess groupings that are absent from normal serum proteins.

Bence Jones protein is antigenically related to the patient's homologous abnormal serum protein and, to a lesser degree, to normal gamma globulin.[4] These urinary proteins are demonstrable in the sera of patients who excrete them. With antisera to normal gamma globulin it was shown that those patients who excrete Bence Jones proteins can be placed in two groups: A) those whose urines contain a single protein, and B) those whose urine contains two Bence Jones proteins, both of which are antigenically distinguishable from A. There is very good evidence that the antigenic difference is a function of the terminal N-amino acid composition of these proteins.[4]

Bence Jones proteins are antigenically more deficient than the corresponding serum globulins and contain some antigenic groupings of these globulins that are absent from normal gamma globulin.

Our studies of the antigenic properties of these proteins have resulted in a simple immunologic test for multiple myeloma.[5]

REFERENCES

1. Ouchterlony, O. Antigen-antibody reactions in gels: IV. Types of reactions in coordinated systems of diffusion, *Acta path. microbiol. scand. 32*:231-40, 1953.
2. Korngold, L. Immunological cross-reactions studied by the Ouchterlony gel diffusion technique: Theory and practice, *J. Immunol. 77*: 119-22, 1956.
3. Korngold, L. and Lipari, R. Multiple-myeloma proteins: I. Immunological studies, *Cancer 9*: 183-92, 1956.
4. Korngold, L. and Lipari, R. Multiple-myeloma proteins: III. The antigenic relationship of Bence Jones proteins to normal gamma-globulin and multiple-myeloma serum proteins, *Cancer 9*:262-72, 1956.
5. Korngold, L., Van Leeuwen, G. and Engle, R. L. The diagnosis of multiple-myeloma and macroglobulinemia by the Ouchterlony gel diffusion technique. Manuscript in preparation.

DISCUSSION

PHILIP G. H. GELL (Birmingham, England): I have done some of the same sort of thing that Dr. Korngold has, some thousands of miles away, and on a very much more limited scale. Our findings are in agreement with essentially everything he has said in regard to cross-reactions, the relationships of gamma globulins, and so on. As well as using this type of technique, we have used the immunoelectrophoretic method of Grabar and Williams, which combines electrophoresis with immunologic analysis.

LEONHARD KORNGOLD: We used a method which is essentially similar: first the proteins are separated by zone electrophoresis on starch; then the starch block is cut into one centimeter strips and the proteins are eluted and concentrated. Each

fraction can then be tested by the Ouchterlony technique.

PHILIP G. H. GELL: The reason I referred to that method was that it enables you to deduce things from the shape of the gamma globulin line. With normal gamma globulin, reacting with antiserum to normal gamma globulin, the line is slightly curved; with myeloma protein reacting with the same antiserum you get a much sharper curve, corresponding to a sharply defined spot of protein, and that is very characteristic.

One small point I would like to mention is about the specificity of this myeloma protein. Just before I left England we found that when very high concentrations of gamma-one globulin were present in the pathologic sera, in all sorts of different kinds of cases, such as liver disease, or disseminated lupus, such sera were apt to cross-react with an antiserum to a beta-myeloma; I did not do enough testing to verify this, but I wonder if Dr. Korngold has tested any other pathologic sera, especially of that type.

I feel in general that the use of these gel-diffusion methods has opened a very wide field of investigation, and I must say that I feel that Dr. Korngold is to be congratulated on the imaginative and critical use he has made of these techniques; for they do need to be treated very critically.

LEONHARD KORNGOLD: We have tested sera from patients with various forms of electrophoretically diffuse hyper-gamma-globulinemia: cirrhosis, lupus, endocarditis, and Boeck's sarcoid, but in these sera the gamma globulin could not be differentiated from the normal. The only proteins that cross-react with spur formation are those in the sera of patients with multiple myeloma, and this reaction seems therefore to be very specific.

We have immunized rabbits against a beta-myeloma globulin, and the antisera obtained at the first bleeding failed to react with normal gamma globulin, even though they cross-reacted with myeloma globulins of the same antigenic grouping (III) as the immunizing protein. After a second injection of this antigen, the resulting antiserum now also cross-reacted with normal gamma-globulin. The properties of your antiserum depend to a large degree on the concentration of the major and minor antigenic groupings on the proteins used for immunization, and how the rabbits react to them.

SIGMUND L. WILENS: In some cases of multiple myeloma there is considerable renal damage; in other cases there is very little. Does this make any difference in the type of globulins you find in the serum of these patients?

LEONHARD KORNGOLD: I do not know. I think that patients with multiple myeloma whose serum pattern is normal excrete Bence Jones proteins in the urine.

SIGMUND L. WILENS: You don't think that the types I, II, or III that you have distinguished are related in any way to abnormal renal function?

LEONHARD KORNGOLD: I do not know.

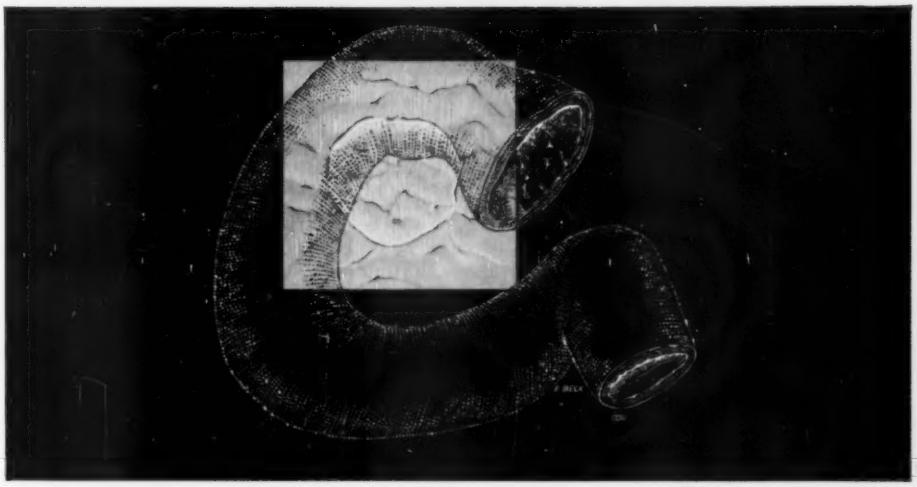
CHANDLER A. STETSON, Jr.: In how many patients with the diagnosis of multiple myeloma do you fail to find detectable abnormal protein in the serum?

LEONHARD KORNGOLD: Approximately 3 to 4 per cent of the sera from myeloma patients will be normal or actually have hypo-gammaglobulinemia, but they usually excrete Bence Jones protein.

CHANDLER A. STETSON, Jr.: In the mouse lines of multiple myeloma, is there Bence Jones proteinemia and is this associated with Bence Jones proteinemia, as in your patients?

LEONHARD KORNGOLD: As far as I know, Bence Jones proteins are not excreted in the urine of mice who carry the transplantable plasmacytoma tumors; at late stages of the disease proteinuria may develop, but according to Dr. Elliot Osserman it is due to the serum proteins.

RELIEVES THE GNAWING ACHE



Pro-Banthīne® provides rapid control of pain in peptic ulcer

In a two-year study[1] by Lichstein and coworkers, documented by intensive personal observation and by follow-up studies, Pro-Banthīne (brand of propantheline bromide) often brought immediate relief of ulcer pain. Patients (11 per cent) who did not respond satisfactorily to Pro-Banthīne therapy had "anxiety manifestations of psychoneurotic proportions."

In addition to frequent immediate symptomatic relief, Pro-Banthīne reduces gastrointestinal motility and diminishes the secretion and acidity of gastric juice, all-important factors in the generation and aggravation of peptic ulcer.

These actions of Pro-Banthīne and its demonstrated effectiveness in accelerating ulcer healing[2-5] mark the drug as a most valuable adjunct in the treatment of peptic ulcer.

The suggested initial dosage is one 15-mg. tablet with meals and two tablets at bedtime. An increased dosage may be necessary for severe manifestations and then two or more tablets four times a day may be prescribed.

G. D. Searle & Co., Chicago 80, Illinois. Research in the Service of Medicine.

---

1. Lichstein, J.; Morehouse, M. G., and Osmon, K. L.: Am. J. M. Sc. *232*:156 (Aug.) 1956.

2. Sun, D. C. H., and Shay, H.: Arch. Int. Med. *97*:442 (April) 1956.

3. Rafsky, H. A.; Fein, H. D.; Breslaw, L., and Rafsky, J. C.: Gastroenterology *27*:21 (July) 1954.

4. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: Gastroenterology *25*:416 (Nov.) 1953.

5. Silver, H. M.; Pucci, H., and Almy, T. P.: New England J. Med. *252*:520 (March 31) 1955.

SEARLE

standardized calibration

The reliability of a blood pressure determination depends upon the standardized calibration of the sphygmomanometer. Similarly, the reliability of urine-sugar testing depends upon the standardization of the testing method.

color-calibrated CLINITEST®

BRAND urine-sugar test

STANDARDIZED READING: full color calibration...blue-to-orange spectrum long familiar to patients and physicians...clear-cut color reactions...unvarying, laboratory-controlled color scale.

STANDARDIZED "PLUS" SYSTEM: established "plus" system...covers entire critical range—does not omit ¾% (++) and 1% (+++).

STANDARDIZED SENSITIVITY: CLINITEST is adjusted to optimal sensitivity...avoids confusing "trace" reactions.

CLINITEST is a copper-reduction test—a 15-year standard for urine-sugar testing "...which is easier than Benedict's...and more accurate...."[1] "The simplicity, speed and accuracy of the Clinitest tablet reagent make it a desirable procedure for quantitation of urinary sugar."[2]

references: 1. Carne, S.: Brit. M. J. 2:827 (Oct. 6) 1956.
2. Giordano, A. S.; Pope, J. L., and Hagan, B.: Am. J. M. Technol. 22:29. 1956.

AMES COMPANY, INC • ELKHART, INDIANA • Ames Company of Canada, Ltd., Toronto

22557

FOR THE ENTIRE RANGE OF RHEUMATIC-ARTHRITIC DISORDERS—from the mildest to the most severe

many patients with **MILD** involvement can be effectively controlled with

'MEPROLONE'

many patients with **MODERATELY SEVERE** involvement can be effectively controlled with

'MEPROLONE'

NEW

and NOW for patients with SEVERE involvement

MULTIPLE COMPRESSED TABLETS

'MEPROLONE'

The first meprobamate-prednisolone therapy

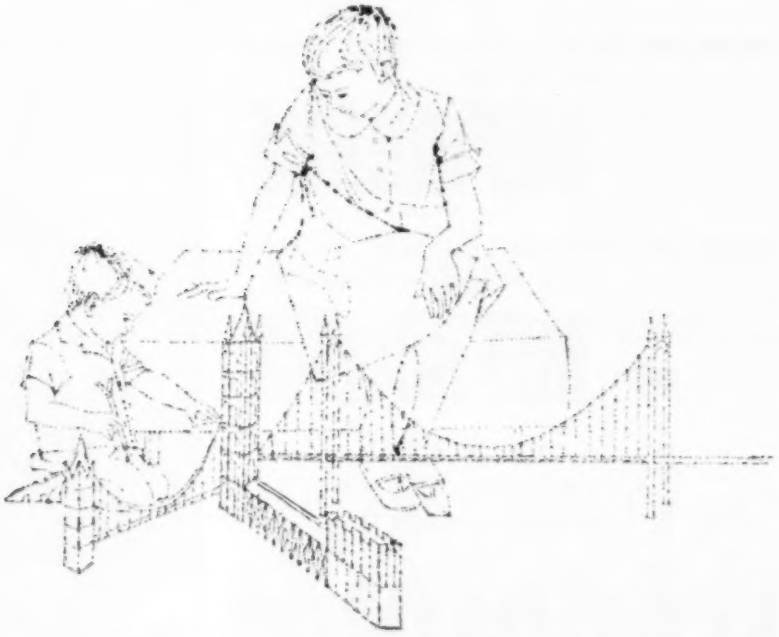
the one antirheumatic, antiarthritic that simultaneously relieves: (1) muscle spasm (2) joint inflammation (3) anxiety and tension (4) discomfort and disability.

SUPPLIED: Multiple Compressed Tablets in three formulas: 'MEPROLONE'-5—5.0 mg. prednisolone, 400 mg. meprobamate and 200 mg. dried aluminum hydroxide gel. 'MEPROLONE'-2—2.0 mg. prednisolone, 200 mg. meprobamate and 200 mg. dried aluminum hydroxide gel. 'MEPROLONE'-1 supplies 1.0 mg. prednisolone in the same formula as 'MEPROLONE'-2.

MSD **MERCK SHARP & DOHME**
DIVISION OF MERCK & CO., INC.
PHILADELPHIA 1, PA.

'MEPROLONE' is a trademark of Merck & Co., Inc.

she needs support, too...
during pregnancy and throughout lactation



NATABEC® KAPSEALS®

vitamin-mineral combination

She balances her nutritional needs by adding to her diet NATABEC Kapseals prescribed by her physician. As a dietary supplement, NATABEC provides vitamins and minerals for nutritional support, helping to promote better present and future health for the mother and her child.

each NATABEC Kapseal contains:

Calcium carbonate	600 mg.
Ferrous sulfate	150 mg.
Vitamin D	400 units
Vitamin B_1 (thiamine) mononitrate	3 mg.
Vitamin B_2 (riboflavin)	2 mg.
Vitamin B_{12} (crystalline)	2 mcg.
Folic acid	1 mg.
Synkamin® (vitamin K) (as the hydrochloride)	0.5 mg.
Rutin	10 mg.
Nicotinamide (niacinamide)	10 mg.
Vitamin B_6 (pyridoxine hydrochloride)	3 mg.
Vitamin C (ascorbic acid)	50 mg.
Vitamin A	4,000 units
Intrinsic factor concentrate	5 mg.

dosage

As a dietary supplement during pregnancy and throughout lactation, one or more Kapseals daily. Available in bottles of 100 and 1,000.

PARKE, DAVIS & COMPANY
DETROIT 32, MICHIGAN

56178

in arthritis, BUFFERIN® because . . .

. . . in the majority of your arthritic cases BUFFERIN alone can safely and effectively provide adequate therapeutic control without resorting to the more dangerous cortisone-like drugs.

. . . BUFFERIN is better tolerated by the stomach than aspirin, especially among arthritics where a high dosage, long term salicylate regimen is indicated.

. . . BUFFERIN provides more rapid and more uniform absorption of salicylate than enteric-coated aspirin.

. . . even in the relatively few cases where steroids are necessary, use of BUFFERIN will allow proper flexibility for individual dosages.

. . . BUFFERIN is more economical for the arthritic who requires a long period of medication.

. . . BUFFERIN *contains no sodium,* thus massive doses can be safely given without fear of sodium accumulation or edema.

Each sodium-free BUFFERIN tablet contains acetylsalicylic acid 5 grains, and the antacids magnesium carbonate and aluminum glycinate.

Bristol-Myers Company, 19 West 50 Street, New York 20, New York

Keep the "reducer" happy

'METHEDRINE'®

in OBESITY

means help

- For those who eat too much
- For those who are depressed

'Methedrine' dispels abnormal craving for food, subtly elevates the mood.

'Methedrine'® brand Methamphetamine Hydrochloride Tablets 5 mg., scored

BURROUGHS WELLCOME & CO. (U. S. A.) INC., Tuckahoe, New York

Vita-Metrazol

reactivates

where apathy is the dominating symptom

Contains Metrazol, Vitamins B_1, B_2, B_6, niacinamide, panthenol, and 15% alcohol in a wine-like flavored elixir.

Average Dose: 2 teaspoonfuls *Vita*-Metrazol 3 or 4 times daily.

Metrazol®, brand of Pentylenetetrazol, E. Bilhuber, Inc.

KNOLL PHARMACEUTICAL COMPANY ORANGE NEW JERSEY

THEO. E. OBRIG, INC.

specialists in fitting contact lenses for more than a quarter century

Theo. E. Obrig, Inc. fits contact lenses only upon prescription and under the supervision of a physician.

Expert in fitting all types of contact lenses including Lacrilens® and latest forms of cornea lenses.

Lacrilens® and corneal type lenses can be worn for long periods of time in aphakia.

Lacrilens® is particularly recommended for all sports including swimming.

Careful attention to referred cases.

Theo. E. Obrig, Inc.
49 East 51st Street
New York 22, N. Y. *PLaza 8-0973*

more than 8,823,769 prescriptions* attest the effectiveness of Veratrite®

• lowers blood pressure gradually • induces a sense of well-being • negligible, if any, side effects

Veratrite is particularly suited to the long term management of mild and moderate hypertension. It improves circulation to vital organs, relieves headaches and dizziness and induces a sense of well-being without excessive euphoria. Furthermore, Veratrite now contains cryptenamine – a newly isolated alkaloid fraction – which lowers blood pressure with unusual safety and without annoying side effects.

Each Veratrite tabule contains:

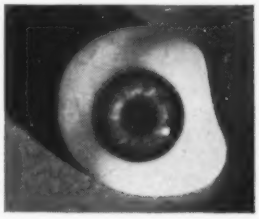
Cryptenamine (tannates)	40 C.S.R.† Units
Sodium nitrite	1 gr.
Phenobarbital	¼ gr.

†Carotid Sinus Reflex

*The number of patients treated successfully with these prescriptions would fill the Rose Bowl 88 times.

For prescription economy, prescribe in 100's. **To serve your patients today . . .** call your pharmacist for any additional information you may need to help you prescribe Veratrite.

IRWIN, NEISLER & CO., DECATUR, ILLINOIS



SATISFACTION GUARANTEED

Specialists in Plastic and Glass Artificial Human Eyes Exclusively

Referred Cases Carefully Attended

FRIED & KOHLER, Inc.

665 FIFTH AVENUE near 53rd Street

NEW YORK, N. Y. Tel. ELdorado 5-1970

PROTEIN-BOUND IODINE

TOTAL IODINE

PAPER ELECTROPHORESIS

CATECHOL-AMINES

STEROID CHEMISTRY

CLINICAL CHEMISTRY

BOSTON MEDICAL LABORATORY

Directors

JOSEPH BENOTTI NORBERT BENOTTI

Medical Director

FRANCESCA M. RACIOPPI, M.D.

19 Bay State Road

Boston 15, Mass.

CO 6-3402

PROMPT SERVICE

PSORIASIS

Proved Clinically Effective Oral Therapy—
maintenance regimen may keep patients lesion-free.

COMPLETE LITERATURE AND REPRINTS
UPON REQUEST. JUST SEND AN Rx BLANK.

LIPAN®

LIPAN Capsules contain: Specially prepared highly activated, desiccated and defatted *whole* Pancreas: Thiamin HCl, 1.5 mg. Vitamin D, 500 I.U.

Available: Bottles 180's, 500's.

Spirt & Co., Inc.
WATERBURY, CONN.

©Copyright 1956 Spirt & Co.

MONTHLY PANEL MEETINGS FOR THE GENERAL PHYSICIAN

Sixth Series — 1957-1958

(Please Note: For the coming academic year these meetings will be held on the SECOND TUESDAY *of the month, November 1957 through April 1958, at 4:30 p.m., in Room 20 at the Academy.)*

TUESDAY December 10 1957	MANAGEMENT OF SURGICAL CONDITIONS OF THE ALIMENTARY TRACT IN INFANCY *Moderator:* George H. Humphreys II
TUESDAY January 14 1958	RECENT ADVANCES IN THE TREATMENT OF THE SPRUE SYNDROME *Moderator:* Thomas P. Almy
TUESDAY February 11 1958	COMMON UROLOGICAL PROBLEMS IN GENERAL PRACTICE *Moderator:* Victor F. Marshall
TUESDAY March 11 1958	MANAGEMENT OF HEMORRHAGIC STATES *Moderator:* Louis R. Wasserman
TUESDAY April 8 1958	EVALUATION AND MANAGEMENT OF FATIGUE *Moderator:* To be announced

THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street • New York 29, N. Y.

now . . . not only the **latest**
but the **best, functional** package
for a **superior** product

AIR-TIGHT
LINER
. . . Keeps soda lime at peak efficiency. The combination polyethylene, aluminum foil and kraft paper lining prevents loss of moisture and protects soda lime from absorbing carbon dioxide.
PUSH-PULL SPOUT
3 LBS.
4897
Soda lime
Mallinckrodt
SODA LIME INDICATING U.S.P.
HIGH-MOISTURE 4-8 MESH
(Contains approximately 15% moisture with Clayton Yellow as indicator)

HANDY "PUSH-PULL" OPENING SPOUT . . . is specially designed to assure free-flowing action of soda lime.

STURDY CONSTRUCTION . . . prevents damage in shipping. Modern design and distinctive color of box make it easily identified.

Mallinckrodt®

INDICATING SODA LIME

for use in Rebreathing Techniques, Metabolism Determinations, and Oxygen Therapy

Mallinckrodt research has achieved the ideal soda lime blend of 4-8 mesh particles — with highly porous, knobby, popcorn-like granule characteristics. This blend permits optimum carbon dioxide absorption efficiency and minimum resistance to gas flow through a filled canister.

Send for your copy of the Mallinckrodt SODA LIME HANDBOOK

Mallinckrodt Chemical Works

SECOND & MALLINCKRODT STREETS, ST. LOUIS 7, MO. • 72 GOLD STREET, NEW YORK 8, N. Y.
CHICAGO • CINCINNATI • CLEVELAND • DETROIT • LOS ANGELES • PHILADELPHIA • SAN FRANCISCO
IN CANADA: **MALLINCKRODT CHEMICAL WORKS LIMITED** • MONTREAL • TORONTO

Neo-Synephrine now has three complementary compounds added to its own dependable, decongestive action for more complete control of the common cold syndrome.

The "syndromatic" action of Neo-Synephrine Compound Cold Tablets brings new and greater effectiveness to the treatment of the common cold syndrome.

protection... through the full range of common cold symptoms

Each tablet contains:

for **NASAL STUFFINESS, TIGHTNESS, RHINORRHEA**

NEO-SYNEPHRINE HCl 5 mg...... First choice in decongestants for its mild but durable action and excellent tolerance.

for **ACHES, CHILLS, FEVER**

ACETAMINOPHEN 150 mg. ..... Dependable analgesic and antipyretic

for **RHINORRHEA, ALLERGIC MANIFESTATIONS**

THENFADIL® HCl 7.5 mg. ..... Effective antihistaminic to relieve rhinorrhea and enhance mucosal resistance to allergic complications.

for **LASSITUDE, MALAISE, MENTAL DEPRESSION**

CAFFEINE 15 mg.

DOSE: ***Adults:*** 2 tablets three times daily.
Children 6 to 12 years: 1 tablet three times daily.

Bottles of 100 tablets.

Neo-Synephrine (brand of phenylephrine) and Thenfadil (brand of thonzylamine), trademarks reg. U.S. Pat. Off.

Winthrop LABORATORIES - NEW YORK 18, N. Y.

One drug . . . of far-ranging versatility

for wide areas of medicine and surgery

These Actions

- Psychic sedative
- Antiemetic
- Antihistaminic
- Analgesic and narcotic potentiating

These Uses

- Nausea and vomiting
- Motion sickness
- Surgical sedation
- Obstetrical sedation
- Allergic reactions
- Oral surgery and dental procedures

These Areas of Practice

- General practice
- Anesthesiology
- Surgery
- Obstetrics
- Allergy
- Pediatrics
- Geriatrics
- Dentistry

Comprehensive literature is available on request.

PHENERGAN® HYDROCHLORIDE

Promethazine Hydrochloride, Wyeth

INJECTION

TABLETS

SUPPOSITORIES

Wyeth

Philadelphia 1, Pa.

Herald Square, N Y

Parkchester, Bronx *Jamaica, Queens*

White Plains, N. Y *Flatbush, Brooklyn*

MACY'S PRESCRIPTION DEPARTMENT

Macy's is accurate. Our Prescription Department is a modern, sanitary laboratory, staffed by competent pharmacists. All of our completed prescriptions are carefully checked by supervising pharmacists. Our stock of ingredients is wide and reliable; it includes not only standard drugs, but also new and scarce products. And our prices are low.

No wonder so many physicians prefer Macy's Prescription Department.

For acidosis due to anesthesia — edema

KALAK

Counter-Acts

ANTI-BIOTIC REACTIONS

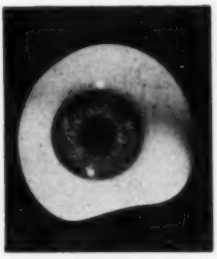
. . . . KALAK is a non-laxative, alkaline diuretic buffer — side reactions from aureomycin — terramycin — sulfas — penicillin are reduced through the use of KALAK — KALAK contains only those salts *NORMALLY* present in plasma. . . . IT IS BASIC!

KALAK WATER CO. of NEW YORK, Inc.

207 EAST 37TH STREET
New York 16, N. Y.

For acidosis due to nausea — in nephritis

PLASTIC AND GLASS EYES



MAGER & GOUGELMAN, Inc.

OVER A CENTURY OF SERVICE • 1851-1957

- PRIVATE FITTINGS
- PERSONAL ATTENTION
- EXPERIENCE & SKILL

120 East 56th St., N. Y. 22
Telephone PLaza 5-3756

EVERY WOMAN
WHO SUFFERS
IN THE
MENOPAUSE
DESERVES
"PREMARIN"

widely used
natural, oral
estrogen

AYERST LABORATORIES
New York, N. Y. • Montreal, Canada
5646

in very special cases
a very superior brandy...
specify
★ ★ ★
HENNESSY
COGNAC BRANDY
84 Proof | Schieffelin & Co., New York

BULLETIN
THE NEW YORK ACADEMY OF MEDICINE

The Bulletin contains scientific papers presented at the Academy, including . . .

Post-Graduate Week Lectures
Stated Meeting Addresses of the Academy
Academy Section Papers
Section on Microbiology—Abstracts
Monthly Panel Meetings—Transcripts
New York Pathological Society—Abstracts
and
Other Original Contributions

Published Monthly
Annual subscription price, $8.00 in United States and Canada.
All other countries $9.00

New Chemotherapy of RHEUMATOID ARTHRITIS

Long-term studies in this country and abroad have shown that the antimalarial **ARALEN** *phosphate produced major improvement in 72% of 294 cases of rheumatoid arthritis. Aralen was often successful where other agents failed. Remissions often persisted for many months after therapy had been discontinued.*

JOINT EFFECTS:

Pain and tenderness relieved. Mobility increased. Swellings diminished or disappeared. Muscle strength improved. Rheumatic nodules often disappeared. Even severe or advanced deformity improved. *Active* inflammatory process usually subsided and joint effusion diminished.

GENERAL EFFECTS:

Patients felt and looked better. Exercise tolerance increased. Walking speed and hand grip improved.

LABORATORY EFFECTS:

E. S. R. often fell slowly and hemoglobin level rose gradually.

ANALGESICS AND STEROIDS

Requirements usually reduced or eliminated.

Dosage: Aralen is cumulative in action and requires four to twelve weeks of administration before therapeutic effects become apparent. The usual adult dose is 250 mg. daily. If side effects appear withdraw Aralen for several days until they subside. Reinstate treatment with 125 mg. daily and, if well tolerated, increase to 250 mg.

If medication is withdrawn, a relapse, if it occurs, will usually be manifest within 3 to 12 months. Resumption of therapy, as above, is generally again effective.

Supplied:

Aralen phosphate: 250 mg. tablets in bottles of 100 and 1000.
125 mg. tablets in bottles of 100.

Write *for booklet discussing clinical experience, tolerance, precautions, etc., in detail.*

ARALEN® PHOSPHATE

Aralen (brand of chloroquine)
trademark reg. U.S. Pat. Off.

Winthrop LABORATORIES
NEW YORK 18, N.Y.

24 steps to a hospital bed

The commonest task, such as climbing a flight of stairs, confronts the angina pectoris patient with a fearful question: *"Will I be able to make it?"*

Exertion leads to attacks . . . and fear of attacks leads to an increasing restriction of activities. Ultimately, even the attack-free intervals may lose all semblance of normal living.

Remove the fear factor. In 4 out of 5 patients, routine prophylaxis with Peritrate reduces the incidence and severity of anginal attacks, improves abnormal EKG tracings and increases exercise tolerance.

A new sense of freedom restores the "cardiac cripple" to a sense of usefulness and participation, although he should not now indulge in previously prohibited strenuous exercise.

Peritrate prophylaxis is simple: 10 or 20 mg. *before meals* and at bedtime. The specific needs of most patients are met with Peritrate's five convenient dosage forms: Peritrate 10 mg. and 20 mg. tablets; Peritrate Delayed Action (10 mg.) for protection continued through the night; Peritrate with Phenobarbital (10 mg. with phenobarbital 15 mg.) where sedation is also required; Peritrate with Aminophylline (10 mg. with aminophylline 100 mg.) in cardiac and circulatory insufficiency.

Usual Dosage: A continuous schedule of 10 to 20 mg. *before meals* and at bedtime.

Peritrate®

(brand of pentaerythritol tetranitrate)

WARNER-CHILCOTT

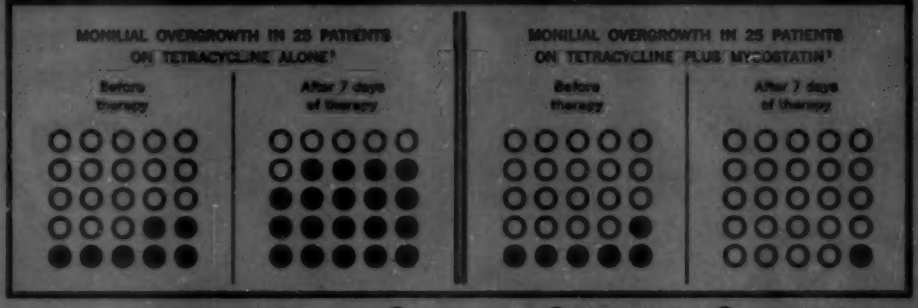
100 YEARS OF SERVICE TO THE MEDICAL PROFESSION

Now...victory over infections

- ***pharmacodynamically superior***
- ***therapeutically unsurpassed***

With Mysteclin-V you get faster and greater absorption of tetracycline than ever attainable in the past . . . providing all the benefits of well-established tetracycline therapy. For practical purposes, Mysteclin-V is sodium-free.

MYSTECLIN-V



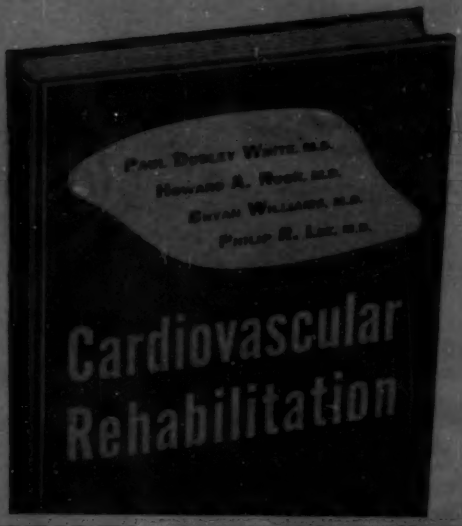
Mycostatin in Mysteclin-V prevents gastrointestinal monilial overgrowth, thereby minimizing the possibility of antibiotic-induced monilial superinfection.

Supply	Tetracycline phosphate complex, equiv. to tetracycline HCl (mg.)	Mycostatin (units)	Packaging
Capsules (per capsule)	250	250,000	Bottles of 16 and 100
Half Strength Capsules (per capsule)	125	125,000	Bottles of 16 and 100
Suspension (per 5 cc.)	125	125,000	2 oz. bottles
Pediatric Drops per cc.—20 drops	100	100,000	10 cc. bottles with dropper

1. Childs, A. J.: [illegible]

SQUIBB *Squibb Quality—the Priceless Ingredient*

PAUL DUDLEY WHITE, M.D., HOWARD A. RUSK, M.D.
BRYAN WILLIAMS, M.D., PHILIP R. LEE, M.D.



have edited a NEW book just off press

Cardiovascular Rehabilitation

CONTENTS

1. Emotions and the Person with Cardiovascular Disease
2. Work and the Person with Cardiovascular Disease
3. The Practice of Cardiovascular Rehabilitation
4. The Teaching of Cardiovascular Rehabilitation
5. Research in Cardiovascular Rehabilitation

WRITTEN in an interesting discussion style, this book is the recorded report of a conference held at the New York University-Bellevue Medical Center under the sponsorship of the Institute of Physical Medicine and Rehabilitation, and supported by a grant from the National Heart Institute, National Institutes of Health.

THIS new book presents the major problems facing the practicing physician in the management and rehabilitation of his cardiovascular patients. From the viewpoints of the participants' experiences, the book considers the areas of recent and future research in or related to cardiovascular rehabilitation. The editors have provided an analysis of the emotions of persons with cardiovascular disease; the types of work the cardiovascular patient can perform; the role of the physician, the public, health agencies in rehabilitation; and the teaching of cardiovascular rehabilitation.

Blakiston Div., McGraw-Hill Book Co.
330 West 42nd St., New York 36, N. Y.

You may send me on 10 day approval:

White, Rusk, Williams, Lee
Cardiovascular Rehabilitation . . $6.50

Name_____

Address_____

City_____ State_____

SHOULD prove useful to general practitioners, internists, cardiologists, physical medicine and rehabilitation specialists, occupational medicine specialists, and industrial health specialists. 155 pp., 5⅜ x 8, $6.50.

FILL IN AND
MAIL COUPON TODAY.